PROTOCOL TITLE:

Testing the ability of JNJ-18038683, a selective serotonin $(5\text{-HT})_7$ antagonist, to improve cognition and reduce residual depressive symptoms in stable bipolar patients (18038683BCD2001)

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1.0 Objectives

The goals of this study are to evaluate the efficacy of JNJ-18038683 in an 8 week trial to ameliorate the cognitive deficit and reduce residual depressive symptoms in 60 stable bipolar outpatients receiving treatment for depression. JNJ-18038683 will be studied and compared with placebo as adjunctive treatment to standard pharmacologic treatment for bipolar disorder.

2.0 Background

2.1.1 Cognitive impairment in bipolar disorder

Most, but not all, patients with bipolar disorder (BPD) have clinically significant cognitive impairment [1, 2]. Impairment is present in both the manic and depressed phases of BPD, as well as in euthymic periods [3]. The percentage of BPD patients with cognitive impairment (CIBD) varies among studies, with 40-60% representing the best estimate [3]. The weight of the evidence supports no overall difference in the type and severity of cognitive impairment in any phase of BPD, i.e. it is a stable trait feature of BPD, albeit variable from one patient to another. The most commonly affected cognitive domains are speed of processing, declarative memory, attention and working memory [3, 4]. Although CIBD is milder in severity than the cognitive impairment associated with schizophrenia (CIAS), on average, as in schizophrenia, CIBD has a major impact on function and quality of life in most patients, particularly because the greater preservation of function of BPD enables them to engage in activities which are more dependent on intact cognitive function [5]. Thus, it is highly likely that improvement in CIBD will have valuable clinical benefit, especially with regard to quality of life measures. It is reasonable to predict that treatments effective to improve CIBD could also be beneficial for CIAS. Efficacy for cognitive impairment is likely to be greater in BPD than schizophrenia, because the baseline severity is milder in the former [6] . Despite this strong rationale for targeting CIBD, there has been minimal focus on clinical trials to improve CIBD, perhaps because so many resources have been devoted to the effort to treat CIAS, but lack of appreciation of the severity of CIBD and its importance as a determinant of functional outcome in BPD may be the most important factors.

In a recent study of CIBD, using the MATRICS Consensus Cognitive Battery (MCCB), impairment was found in both treatment resistant BP I and II depressed inpatients within all MCCB domains [4]. The greatest impairment was evident in speed of processing, declarative memory and attention. The impairment was numerically greater in BP I than BP II patients but the difference was not significant. Compared to normal controls, the deficits, in BP 1 patients, in speed of processing was 1.2SD, in attention, 1.0 SD, and in verbal learning, 1.8 SD. The least affected domain was visual learning, with a mean deficit of 0.8SD compared to normal controls. The mean composite score deficit was 1.25 SD. Medication for BPD, particularly mood stabilizers, may adversely affect some domains of cognition in

BPD [7]. However, antidepressant medications have not been found to affect the severity of cognitive impairment in major depression or BPD [8].

2.1.2 Preclinical Rationale for Studying JNJ-18038683 to treat CIBD and CIAS

Serotonin $(5\text{-HT})_7$ receptors are one of 14 5-HT receptors. This Gs-protein coupled receptor is widely distributed in brain, with high density in the thalamus, hypothalamus, hippocampus, suprachiasmatic nucleus, amygdala and septum, with lower levels in the cerebral cortex. The HTR7, is positively coupled to adenylate cyclase (as are the dopamine (DA) D_1, 5-HT_4 and 5-HT_6 receptors), and has aroused considerable interest as a target for drugs to treat depression, as well as some for cognitive impairment and psychosis [9-11]. For example, there has been considerable interest in 5-HT_7 antagonists as stand-alone antidepressants [10, 12, 13] or as contributor to multireceptor antidepressant drugs [14-16]. JNJ 18038683 and other selective 5-HT_7 receptor antagonists have been reported to be effective antidepressants in a variety of animal models, including tail suspension [13]. JNJ-18038683 potentiated the ability of a sub-effective dose of the SSRI citalopram to increase extracellular levels of 5-HT in rat cortex. JNJ-18038683 had no effect by itself on 5-HT efflux in a microdialysis study. In a failed clinical trial, JNJ-18038683 did not differentiate from placebo, but the active comparator also did not differentiate, possibly because of a high placebo response rate. Importantly, no safety concerns emerged for the compound [13].

Of key relevance to this proposal, 5-HT_7 receptor selective drugs have been shown to be active in animal models of psychosis, learning, and memory [10]. 5-HT_7 receptor blockade has been postulated to be a key component of the cognitive enhancement due to atypical APDs, e.g. amisulpride, clozapine, lurasidone, and risperidone, which are potent 5-HT_7 antagonists [17-19] and as a stand-alone cognitive enhancer [20]. We will report key additional evidence in the Preliminary Studies section. With regard to animal models of antipsychotic activity, the selective 5-HT_7 antagonist, SB-258471, prevented the disruption of prepulse inhibition (PPI) in phencyclidine (PCP)-but not amphetamine-treated rats, indicating positive influence on the glutamate, but not DA, component of PPI, a model of the sensory gating deficit in BPD and schizophrenia which has bearing upon antipsychotic activity and attention, a key component of CIBD [9]. However, the selective, 5-HT_7 antagonist SB269970 [21] was able to reverse the effect of amphetamine to disrupt PPI in C57BL/6 mice [9]. It has been reported that SB-269970 significantly reversed the NMDA receptor antagonist dizocilpline (MK-801)-induced deficits in the delayed non-matching to position task, a measure of working memory, but augmented the deficit induced by low dose scopolamine, a muscarinic antagonist [22]. These authors also showed that SB-269970 normalized MK-801-induced glutamate but not DA efflux in the prefrontal cortex. SB269970 improved reference memory in a radial arm maze [9, 12] and a PCP-induced reversal learning deficit in rats [23]. SB-656104-A, another 5-HT_7

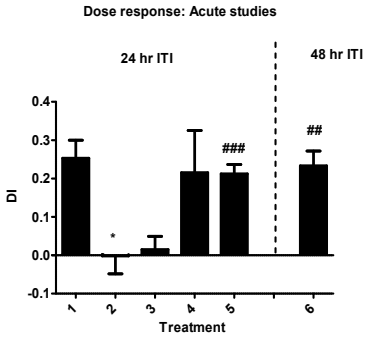
antagonist, improved learning and memory deficits induced by an NMDAR antagonist, in the rat passive avoidance test alone and with a subeffective dose of lurasidone [24]. Sarkisyan and Hedlund [25] reported a deficit in spatial memory in a novel location test in 5-HT_7 knock out mice and mice treated with SB-269970. However, we have found no deficit in novel location in HTR7 knock out mice. In a recent publication, Andressen et al There is some conflicting evidence about the role of 5-HT_7 antagonism in cognition. 5-HT_7 agonism has been suggested to be an effective target for improvement of cognitive impairment in aging mice and in an Alzheimer's mouse model, as the 5-HT_7 agonist AS19 enhanced memory formation in an autoshaping task, an effect blocked by SB269970 [26]. Gasbarri et al [27] suggested that the role of the 5-HT_7 receptor in cognition will vary depending upon the task and brain regions involved. Eriksson et al [28] suggested that 5-HT_7 receptor blockade can intensify impairments in emotional memory that are induced by 5-HT_{1A} receptor stimulation.

2.1.3 Preclinical Evidence:

The predominant strategy to develop pharmacologic treatments for CIAS and by extension, CIBD, relies upon ameliorating cognitive impairment induced in rodent models which have some relation to the psychotic spectrum disorders, especially drug- or transgenic-induced abnormalities in cognition**.** Evidence from animal models suggests that serotonin (5-HT)$_7$ receptor(R) antagonism is a promising target to treat CIBD and CIAS. We have extensively studied SB-269970, the protypical 5-HT_7 selective antagonist, in the sub-chronic (sc) phencyclidine (PCP) rat and mouse models of CIAS. PCP, an NMDAR antagonist, is widely studied for this purpose because of the extensive evidence that abnormalities in glutamate and GABA neurotransmission in cortex and hippocampus may be the prime cause of CIAS. Acute or scPCP produces a wide range of documented deficits in NMDAR and GABA neurotransmission. We recently reported that SB269970 (0.1-1 mg/kg) dose-dependently reversed scPCP-induced novel object recognition (NOR) deficits in rats [17]. NOR is a model of human declarative memory. We have replicated these results in mice treated with PCP or ketamine for 7 days and washed out 7 days or longer (Figure 1). SB-269970 can also reverse PCP-induced deficits in novel location detection. Our data contrasts with results from the Hedlund lab. In addition, we reported that the ability of two atypical antipsychotic drugs (APDs), lurasidone (0.1 mg/kg) and amisulpride (3 mg/kg), to reverse the NOR deficit was blocked by co-treatment with the 5-HT_7 receptor agonist, AS19, (5-10 mg/kg). None of these compounds affect NOR in naive rats. There is also extensive evidence supporting the cognitive benefits from 5-HT_7 receptor blockade from other labs, e.g. restoration of reversal learning in PCP-treated rats. Furthermore, we have been breeding 5-HT_7 knock out mice for a year and now have many studies with these mice which replicate the results with SB-269970, including prevention of the NOR deficit produced by acute or sub-chronic PCP (Figure 2). In addition, the 5-HT_7 knockout mice, from adolescence to adulthood,

show superior duration of memory for NOR compared to wild type mice (Supplemental Figure 1). Figures referenced below include the discrimination index of the NOR experiments, which quantifies the animal's ability to recognize and explore the novel object more than the familiar.

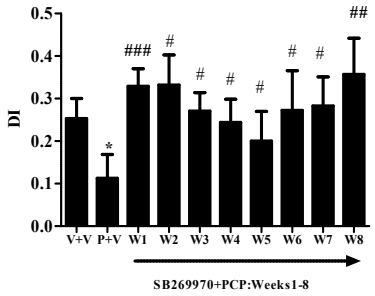
Figure 1: Effect of SB269970 to restore NOR at 24 and 48 hrs after Acquisition



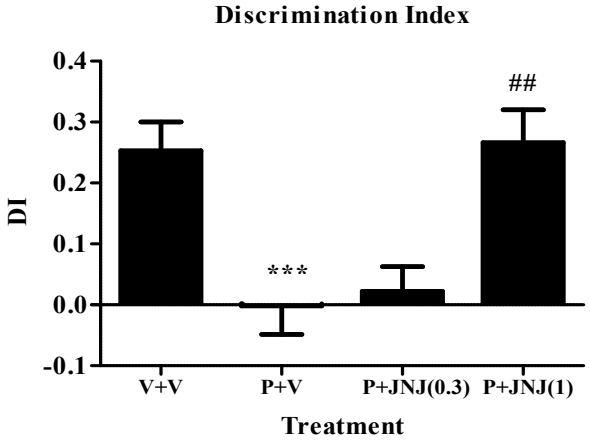
1. Vehicle+vehicle
2. PCP+vehicle
3. PCP+SB269970(0.3 mg/kg): sub-effective dose
4. PCP+SB269970(0.5 mg/kg): partially effective dose
5. PCP+SB269970(1 mg/kg): effective dose
6. PCP+SB269970(1 mg/kg): effective dose - 48 hr ITI

*P<0.05: significant reduction in DI compared to vehicle
##-###P<0.01 - P<0.001: significant increase in DI compared to PCP

Figure 2: SB269970 co-administered with sub-chronic PCP Prevents Deficit in NOR produced by sub-chronic PCP for at least 8 weeks.



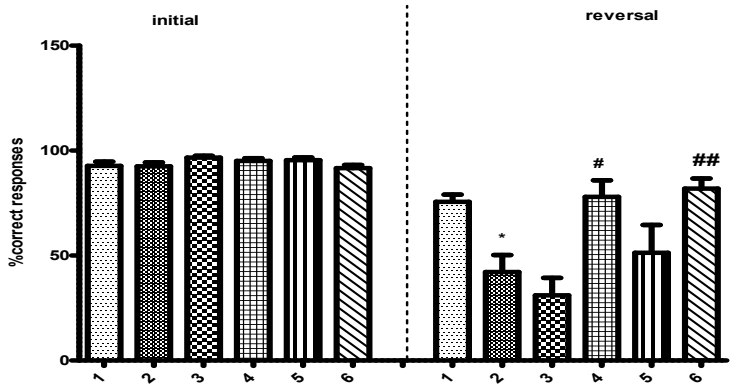
Our lab has also conducted studies with JNJ-18038683 which indicate that it is as effective as SB269970 to restore NOR in scPCP-treated mice (Figure 3).



Additional Evidence for Pro-cognitive effects of JNJ-18038683 on Executive Function:

Reversal learning: See Abdul-Monim et al., and Brigman et al., [29, 30] for detailed methodology**.** Apart from the declarative memory deficits, there is a range of cognitive deficits in BPD and schizophrenia, including impaired executive functioning [31], which can be assessed by operant reversal learning tasks in rodents [32]. We found that both JNJ-18038683 and SB269970 (4 mg/kg) were able to reverse sub-chronic PCP induced decrease in percentage correct responding in the reversal phase of the task (Figure 4).

Figure 4: Effect of 5-HT7 antagonists on executive function in PCP treated animals
Figure 3: Acute reversal of sub-chronic PCP with JNJ-18038683: Determination of effective and sub-effective doses (1.0 mg/kg and 0.3 mg/kg, respectively)



1. Vehicle+vehicle
2. PCP+vehicle
3. PCP+SB269970 (0.5 mg/kg) - sub-effective dose
4. PCP+SB269970 (4 mg/kg) -effective dose
5. PCP+JNJ18038683(1 mg/kg) - sub-effective dose
6. PCP+JNJ18038683 (4 mg/kg)-Effective dose

***P<0.05: significant reduction in percentage correct responding compared to vehicle group; #P<0.5; ##0.01: significant increase in percentage correct responding compared to PCP group.**

2.2 Rationale for Randomized Controlled Trial of JNJ-18038683 on Cognition and Residual Depressive Symptoms in Bipolar Disorder

Based on the pre-clinical, pro-cognitive effects of 5-HT_7 antagonism in our laboratory, along with the reported pre-clinical antidepressant effects of JNJ-18038683, we propose to conduct a randomized, placebo- controlled parallel, design study to assess the effects of JNJ-18038683 on multiple domains of cognition and mood symptoms. Since our preclinical studies show that 5-HT_7 receptor blockade is highly effective in improving declarative memory in rodents, the declarative memory measures will be the primary outcome measures. As previously discussed Andressen et. al [39] noted differential functional selectivity of the 5-HT_7 receptor, suggesting that the effects of atypical APDs with known 5-HT_7 antagonism, such as lurasidone, ziprasidone and risperidone, are modulated via different HTR_7 subunits than JNJ1083868. In light of this new information, we proposed to allow some individuals currently prescribed treatment with atypical APDs with 5-HT_7 antagonism to be eligible for screening and randomization.

Due to the effect of JNJ-18038683 on depressive symptoms in preclinical paradigms [12], we will investigate the following in the clinical trial the potential antidepressant effect of JNJ-18038683 on patients with baseline MADRS score between 8 and 20.

3.0 Inclusion and Exclusion Criteria

All patients will meet criteria for DSM-V diagnosis of Bipolar I or Bipolar II disorder. At the time of enrollment, patients will be relatively stable, and may be in a mild-moderate depressed state. 60 patients will be enrolled, and randomized in a 1:1 ratio to one dose of JNJ-18038683 or placebo. Randomization will be stratified by the presence / absence of atypical APDs with 5-HT_7 antagonism so that there is a balance in the assignment of active treatment and placebo in individuals who are, and are not, receiving atypical APDs with 5-HT_7 antagonism. The percentage of those enrolled that are prescribed these atypical APDs will be 35% of the overall enrollment.

Individuals must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

1. All participants must have signed an informed consent document indicating they understand the purpose of the study and the procedures required for the study and are willing to participate by complying with the study procedures and restrictions.

2. Male or female individuals of any race; between 18 to 60 years of age, inclusive.
3. Resides in a stable living situation, according to the investigator's judgment.
4. Diagnosis of bipolar disorder I or II for at least 1 year in duration, as established by the SCID-I, and verified with medical records and/or confirmation of diagnosis by treating clinician. Patients will be in a nonacute phase at the time of initial screening and have been so for at least 1 month.

5. No more than moderate clinical symptom burden severity, as defined by the following:
    - Montgomery Asberg Depression Rating Scale $\leq$ 20
    - Young Mania Rating Scale $\leq$12
6. Individuals medically stable enough to complete an 8 week clinical trial, in the judgment of the investigator

7. Women of childbearing potential must have a negative pregnancy serum test at screening, negative pregnancy urine test at baseline, and agree to use adequate protection (i.e. double barrier method) for birth control.
8. Antidepressant (AD) medications are allowed if the subject has been treated with a stable dose for at least 2 months before screening.
9. Individuals receiving a single mood stabilizer (e.g., lithium. valproate, or lamictal) are allowed if a stable dose has been maintained for at least 2 months prior to screening.
10. Individuals may be receiving one treatment of each the following groups: antidepressants, mood stabilizers, and atypical antipsychotics other than clozapine, but not more than one from each group.
11. Individuals taking ripseridone, lurasidone, or ziprasidone must be currently taking $\leq$ doses of 3mg, 40mg, and, 80mg, respectively.
12. Subjects may be treated with inclusionary antipsychotic drugs as long as they are on a stable dose of injectable medication for 2 months or a sable dose of an oral medication for 1 month. Exclusionary antipsychotic drugs are listed in Appendix 2.
13. Patients with a history of compliance with a drug treatment regimen for bipolar disorder, as noted in medical/psychiatric history.
14. CNS stimulants (e.g., Adderall, Ritalin) are permitted if the participant is stable on their dosage of medication for 1 month before screening and cannot change dosage throughout the study.
15. Able to complete cognition assessments in English
16. Individuals must demonstrate a substantive cognitive deficit, as measured by the Trails A, Hopkins Verbal Learning Test (HVLT), and the Letter Number Span, administered at the screening visit. Eligible individuals will have an established cognitive deficit as measured by one or more of these tests, scoring below the 75^{th} percentile, using comparative norms according to age, gender, and education.
17. Able to understand and complete cognition assessments

3.2 Exclusion Criteria

1. Failure to perform screening or baseline examinations
2. Hospitalization within 8 weeks before screening, or change in mood stabilizing or antidepressant medication or dose within 2 months prior to screening
3. Individuals who have participated in another clinical study within the past 2 months.
4. Individuals with tardive dyskinesia.
5. Individuals with other DSM-V Axis I or Axis II primary diagnoses.

6. Diagnosis of alcohol or substance use disorder within the past 3 months.
7. Subject assessed to be at significant suicide risk based on responses to the Columbia Suicide Severity Rating Scale (C-SSRS).
8. History of myocardial infarction, unstable angina, uncontrolled hypotension or hypertension within 3 months before screening.
9. Clinically significant abnormality on screening ECG.
10. Alanine transaminase (ALT) or aspartate transaminase (AST) > 2.5 times the upper limit of normal (ULN).
11. History of stroke, brain tumor, head trauma with loss of consciousness, or other clinically significant neurological condition within 12 months before screening.
12. Individuals with other uncontrolled medical conditions, in the opinion of the investigator.
13. Use of drugs known to be metabolized by CYP2D6 (see Appendix 2)

4.0 Study-Wide Number of Individuals

4.1 There will be 60 total participants

5.0 Study-Wide Recruitment Methods

5.1 This is a multi-center study. We will be using referrals directly from the providers and recruitment materials by posting in the clinics. We will utilize referrals from primary care or psychiatry providers, or from participant interest and consent. We will also be recruiting individuals through the NU-SRG Recruitment Pipeline (STU00059328) for the Northwestern University site.

6.0 Multi-Site Research

6.1 This is a multi-center study. There are two study sites where the research procedures will take place: Northwestern University, Chicago, IL and Beacon Medical Group Behavioral Health South Bend, South Bend, IN. Northwestern University will be the coordinating center and Beacon Medical Group Behavioral Health South Bend will be a satellite site.

7.0 Study Timelines

Schedule of Assessments:

Study Day	Screen	1	7	14	21	28	35	42	49	56	84
Event/Assessment					**Phone Call**		**Phone Call**		**Phone Call**		**Phone Call**
Informed Consent	X										
Medical History & Demographics	X										
Physical Examination	X										
Electrocardiogram	X					X				X	
Vital Signs	X	X	X	X		X		X		X	
Clinical Safety Laboratory Tests	X					X				X	
Serum Pregnancy Test	X										
Urine Pregnancy Test		X									
Urine Drug Screen	X										
Inclusion/Exclusion Criteria	X										
SCID-I	X										
Screening neurocognitive assessments	X										
Montgomery Asberg Depression Rating Scale		X				X				X	
SLOF		X								X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
AIMS		X				X				X	
Neurocognitive battery	X	X								X	
CGI-BP		X				X				X	
Young Mania Rating Scale		X				X				X	
Assessment of Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Assessment of Adverse Events	X	X	X	X	X	X	X	X	X	X	X

8.0 Study Endpoints

The declarative verbal memory subscales will be the primary endpoints. Secondary outcome measures will include cognition composite score, the MADRS total score (for those with a MADRS score between 8 and 20 at the time of enrollment) and individual scores for each of the other neuropsychological tests. We will assess JNJ-18038683 effects on functional ability and clinical global severity scores as additional endpoints, as measured by the SLOF and CGI-BP. Further, we will analyze the effect on drug tolerability as determined by the following: body weight, body mass index (BMI), waist circumference, and movement rating scales.

9.0 Procedures Involved

Study visits will include screening and 6 visits (baseline, Weeks 1, 2, 4, 6, and 8). Please see Appendix 1 – Schedule of Assessments

At screening, the Structured Clinical Interview for Diagnosis for DSM Disorders (SCID) will be completed for confirmation of psychiatric diagnosis. A medical/psychiatric history will also be collected and a physical exam will be performed. Vital signs including weight, height, waist and hip measurement will be obtained at screening to record body mass index. The Hopkins Verbal Learning Test (HVLT) and Trail Making Test A (TMT-A), will be administered to screen for severity of cognitive impairment. Only individuals who score between the 25th and 75th percentile as compared to normative data on these tasks will be enrolled.

If the subject is determined eligible during the screening procedure, which can last for up to two weeks, a baseline visit will be scheduled. Baseline assessments of cognitive function, psychopathology and global function will be administered along with movement ratings at the baseline visit. Functional outcome will be assessed with Specific Level of Function Scale (SLOF) [33]. Adverse events will be collected and recorded from the time the subject signs the informed consent to the final safety follow-up visit, and motor side effects will be monitored by the Abnormal Involuntary Movement Scale at the following visits: baseline, Weeks 4 and 8.

Individuals will be randomized to receive JNJ-18038683 or placebo after the completion of the baseline assessments. Individuals will be stratified for randomization as either being treated with an AD or not being treated with an AD. As in the previous study of JNJ-18038683 for depression, individuals randomized to JNJ-18038683 will receive 10 mg for one week, then titrate to 20 mg, with the provision for a single, downward dose adjustment for intolerance, based upon investigator judgment. No antipsychotic drugs which are 5-HT_7 antagonists will be permitted to avoid effects upon 5-HT_7 receptors from enhanced 5-HT concentrations and possible down regulation of 5-HT_7 receptors. As JNJ-18038683 is a competitive inhibitor of CYP2D6, there will be a 2 week washout period requested after the trial prior to initiation of any CYP2D6 substrates (see Appendix 2).

Individuals will be asked to return to the clinic at study weeks 1, 2, 4, and 6 after baseline to monitor for side effects and compliance. At the Week 4 visit, efficacy assessments will be completed (MADRS, YMRS and CGI-BP). Between clinic visits, research staff will complete phone calls with individuals at study Weeks 3, 5, and 7. Individuals will return for a final study visit 8 weeks after initiation of the randomized study medication. A Safety Follow-up phone call will take place 4 weeks after the final visit and safety assessments will be completed (C-SSRS, Adverse Events, Concomitant Medications). The assessments completed at baseline will be repeated at this Week 8 visit (See Appendix 1 – Schedule of Assessments). Reasons for early termination will be recorded. Every effort will be made to obtain appropriate rating scale data at the final visit of early terminators.

9.1 Outcome Measures:

A) Comprehensive cognition battery (measuring executive functioning, speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving)
B) Montgomery Asberg Depression Rating scale
C) Young Mania Rating Scale
D) Clinical Global Impression - BP
E) Columbia Suicide Severity Rating Scale
F) AIMS scale for tardive dyskinesia
G) Specific Level of Functioning
H) Weight, height, waist circumference, triglycerides, FBS, LFTs

9.2 Randomization Method:

Those who meet the study inclusion criteria will be randomized into one of two treatment groups, one to receive adjunctive therapy of JNJ-18038683 and the other to receive placebo. Individuals will be stratified for randomization as either being treated with an AD or not being treated with an AD. Using SAS software, a computer-generated randomization sequences for each treatment arm will be assigned using permuted block method limiting imbalance in numbers between groups. To assign the randomization, the SAS procedure PROC PLAN will be used [34]. Until the trial is concluded, the randomization sequence will be blind to the study participants as well as the Principal Investigator, research coordinators and raters. Randomization list will be provided by assigned statistician, Karu Jayathilake, and will be held by unblinded study drug manager at 680 N. Lakeshore Dr., Suite 1410; Chicago, IL 60611-7101 and at 707 N. Michigan St Suite 400 South Bend, IN 46601 for the Beacon Medical Group Behavioral Health South Bend site.

9.3 Adverse Events

In a 7 week, randomized, placebo controlled trial comparing JNJ-18038683 with placebo and escitalopram (an active comparator), a total of 6 serious adverse events were reported during the study (placebo group: spontaneous abortion and suicidal ideation; escitalopram group: spontaneous abortion, suicidal ideation, suicide attempt, and chest discomfort). A total of 10 individuals (3 in the placebo group, 4 in the JNJ-18038683 group, and 3 in the escitalopram group) were withdrawn from the study prematurely due to adverse events. The 4 events leading to drop out of individuals on JNJ-18038683 were one instance each of the following: bundle branch block, panic attack, upper respiratory infection, and insomnia.
Only 3 individuals receiving the 20-mg dose of JNJ 18038683 required dose reductions at any point during the study.

Adverse events that were reported in more than 5% of individuals in any treatment group included headache, nausea, nasopharyngitis, insomnia, somnolence, dyspepsia, dizziness, dry mouth, constipation, diarrhea, vomiting, back pain, upper respiratory tract infection, palpitations, and fatigue. The treatment-emergent adverse events that were reported more frequently in the JNJ 18038683 group compared with the placebo or escitalopram groups included dyspepsia, constipation, upper respiratory tract infection, and palpitations.

9.3.1 Contraindications:

None known

9.3.2 Special Warnings and Precautions for Use

JNJ-18038683 is an investigational drug, with safety data available from nonclinical animal studies, as well as single and multiple dose clinical studies in healthy volunteers.

All individuals should be closely monitored by means of adverse events, vital signs, ECGs, and clinical laboratory safety tests of blood and urine.

The liver, lung, prostate, mammary gland, hematologic system, and thymus in rats (mainly at high dose), and the hematologic system and spleen in dogs, were identified as potential target organs for JNJ-18038683 in repeat-dose oral toxicity studies (see Other Effects in Investigator Brochure). Female animals appeared to be more susceptible than males.

Thus far in clinical trials, there have been no laboratory abnormalities of concern, but the following safety tests should be monitored:

- Hematologic parameters: red blood cell (RBC), hemoglobin, hematocrit, unconjugated bilirubin, reticulocyte, and platelet counts;
- Liver function: aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyltransferase (GGT), prothrombin time, total bilirubin, lactic dehydrogenase, serum albumin, and protein.

9.3.3 Interaction with other medications

After single and multiple doses of JNJ-18038683, limited or no inhibition of CYP3A4 and CYP2C9 activity may be expected, while moderate inhibition of CYP2C19 activity, and strong inhibition of CYP2D6 activity may be likely. JNJ-18038683 increased the rate of T4 glucuronidation. There was no induction of CYPs 1A2, 3A4, 2C9, and 2C19 by JNJ-18038683.

9.3.4 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of individuals enrolled in the studies as

well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All individuals experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

9.3.5 Definitions

9.3.5.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

9.3.5.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

9.3.5.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in death.**
  - If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- **Is life-threatening.**
  - (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**

- **Results in persistent or significant disability or incapacity.**

- **Is a congenital anomaly/birth defect**

- **Is an important medical event**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

9.3.6 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy Attribution categories are as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the GRAS dossier for the supplement;

9.3.7 Reporting Requirements for Adverse Events

Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

- The investigator or site personnel will inform Janssen within 24 hours of notification of any serious adverse event by phone or fax, with follow-up with a written narrative of the event within 48 hours.

- The Northwestern University Institutional Review Board must be notified within 10 business days of “any unanticipated problems involving risk to individuals or others”

The following events meet the definition of Unanticipated Problem Reporting (UPR):

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to individuals or others, and was possibly related to the research procedures.

2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.

3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.

6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- The FDA will be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually to the Northwestern IRB as part of regular data submission.

9.3.8 Unblinding Procedures

The blind should not be broken unless subject has completed all study procedures and the data has been locked. Emergency unblinding is expected to be infrequent.
Emergency unblinding should occur only if the principal investigator (or other treating physician) considers breaking the blind medically relevant. All individuals who have the blind broken will be discontinued from the study. Documentation of the reasons for unblinding, including date and time will be recorded in the source documents and the electronic case report form (eCRF).

9.4 Study Materials

9.4.1 Structured Clinical Interview for DSM-IV (SCID)

The SCID-CT is a short semi-structured interview. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology. The SCID-CT will be administered by raters at the study site. The SCID-CT must be administered by a site study staff member listed on the site delegation of authority log with at least 2 years of experience with the population under study. The results of this assessment will be used to confirm the diagnosis of bipolar disorder I or II and rule out any exclusionary diagnosis. The SCID will be administered at the screening visit.

9.4.2 Cognition battery

The “Cleveland” cognition battery will be administered in this trial, which the PI has used over the past 30+ years as measures of the following cognitive domains: executive functioning, speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving

This battery includes the following assessments:

- Wisconsin Card Sorting Test (WCST)
- Digit Symbol Task
- Rey Auditory Verbal Learning Test (Rey-AVLT)
- WISC-III Mazes
- Category Fluency Test
- Verbal Fluency
- Brown-Peterson Consonant Trigram Memory Task

The cognition battery will be administered at baseline and end of study.

9.4.3 Montgomery Asberg Depression Rating Scale (MADRS) [35] -

The MADRS will be utilized to assess a subject's level of depressive symptoms and must be administered using a structured interview guide. This scale consists of 10 items each with 7 defined grades of severity

9.4.4 Young Mania Rating Scale (YMRS) [36]-

The YMRS consists of 11 items assessing the core symptoms of mania and is based on the subject's subjective report of his or her clinical condition. Additional information is based upon clinical observations made during the course of the clinical interview. Each item has 5 defined categories of severity with 4 items graded on a 0 to 8 scale (irritability, speech, content, and disruptive-aggressive behavior) and 7 items graded on a 0 to 4 scale.

9.4.6 Clinical Global Impression Scale – Bipolar (CGI-BP) [37] -

The CGI-BP scale refers to the global impression of the subject with respect to bipolar disorder. The scale rates the subject's Severity of Illness (CGI-BP-Severity: mania, depression, and overall bipolar illness) and Change from Preceding Phase (CGI-BP Change from Preceding Phase: mania, depression, and overall bipolar illness) based on a 7-point scale. Severity of Illness (CGI-BP-Severity) will be rated at the baseline visit. The Change from Preceding Phase (CGI-BP Change from Preceding Phase) will be rated at the end of study visit (Week 9).

9.4.7 Specific Levels of Functioning (SLOF) [33] -

The SLOF is a clinician-rated assessment that evaluates functional behaviors in the context of the individual's skills and abilities. It consists of 43 items categorized into 6 subscales: Physical functioning; Personal care skills; Interpersonal relationships; Social acceptability; Activities of community living; and Work skills. Each question is rated on a 5-point scale. The higher the total score, the better the overall functioning of the subject. According to the original version of the scale, the time frame covered by the survey is the past week. While an informant is not required for this trial, access to a person that can provide collateral (caseworker, caregiver, etc.) is preferred, as the SLOF asks them for any other relevant information, and also includes a rating for how well the informant knows the subject. The SLOF will be performed at the baseline and end of study visits.

9.4.8 Physical Examination

The physical exams must be performed by the PI or designee (or a licensed medical practitioner such as a physician's assistant or nurse practitioner) listed on the site delegation of authority log.

A complete physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

9.4.9 Vital Signs

Arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured while the patient is seated at the scheduled visits designated in the Schedule of Events in Appendix 1.

9.4.9.1 Height and Body Weight

Height will be measured at the screening visit. Patients will be measured without shoes. Body weight will be recorded at screening, baseline and every visit through the 9-week treatment phase.

9.4.9.2 Body Mass Index (BMI)

Body mass index (BMI) will be determined with the patient's height and weight at the screening visit and subsequent treatment visits. BMI must be calculated using the following formula: A person's (Weight in pounds divided by their height in inches squared) x 703.

9.4.9.3 Waist and Hip Circumference

Waist and hip circumference will be recorded at screening, baseline, and all study visits.

9.4.10 Electrocardiogram (12-Lead ECG)

The PI or a physician listed on the site delegation of authority log must review, initial, and date the report, which must be filed in the subject's study chart. Results will be captured in the subject's study chart, not in the electronic database. Clinically significant findings from the screening report must be captured in the medical history. Eligibility for study entry must be assessed by the principal investigator. Any clinically significant changes compared with baseline must be captured as AEs in the electronic database.
Individuals are to be supine for at least 5 minutes prior to ECG assessments. A central facility will be used in this study for interpretation and analysis of ECGs. All individuals will have standard resting 12-lead ECGs performed and interpreted. The time the ECG is performed will be recorded (using a 24-h clock). In addition, the time that the subject took their last dose of study medication (prior to the ECG) will be recorded on the CRF page.

9.4.11 Adverse Event (AE) Monitoring

The PI or a designee (eg, a licensed, qualified medical practitioner such as a physician's assistant or a nurse practitioner) listed on the site delegation of authority log must assess the severity and relationship to study medication(s) of all AEs. All observed or volunteered AEs regardless of treatment group or

suspected causal relationship to the investigational product(s) will be recorded on the AE page(s) of the electronic database.
For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.
For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality and indicate that assessment on the source document and electronic database.
For AEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.
Adverse events (serious and non-serious) should be recorded on the source document and electronic medical record from the date the informed consent form (ICF) was signed until the end of their participation in the study, ie, the subject has discontinued or completed the study.

9.4.12 Concomitant Medications

Concomitant Medications will be documented using the Concomitant Medications form at Baseline and all study visits.

9.4.13 Study Medication Adherence

Participants will be asked about his/her medication adherence at each appointment. Study personnel will count and record the number of pills in the patient's study medication bottles and provide immediate feedback, reinforcing the behaviors of patients who appear to be taking medications as prescribed and problem-solving with those who appear not to be. Clinicians will review with patients the use of pill-minder boxes, as needed.

9.4.14 Laboratory Test Assessments

Northwestern Medicine Laboratory and South Bend Medical Foundation will be used for analysis of fasting lab assessments required during the study. Blood will be drawn from each patient at the screening visit, and at end of study as noted in the study Schedule of Events in Appendix 1. The tests will include: Chemistry panels; Hematologic parameters: red blood cell (RBC), hemoglobin, hematocrit, unconjugated bilirubin, reticulocyte, and platelet counts; Liver function: aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyltransferase (GGT), prothrombin time, total bilirubin, lactic dehydrogenase, albumin, protein, creatinine. A urine drug screen (UDS) will be obtained at screening only.
In women of childbearing potential, serum pregnancy testing will occur at screening; urine pregnancy will occur at study baseline.

Note: At screening and throughout study participation, a positive UDS is not necessarily exclusionary and/or may not require a subject be withdrawn from the study. This decision will be per the discretion of the principal investigator.

9.5 Safety Scales

9.5.1 Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk.

9.5.2 Columbia Suicide Severity Rating Scale

The C-SSRS was developed by a team of researchers at Columbia University to address the need for standardized classification of suicide reports to assess suicide risk. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a post-baseline evaluation that focuses on suicidality since the last study visit. A baseline C-SSRS will be completed at the screening visit. The C-SSRS Since Last Visit form will be completed at all subsequent visits and telephone calls (Day 21, Day 35, and Day 49).

10.0 Data and Specimen Banking

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Janssen-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.0 Data and Specimen Management

11.1 Data Analysis Plan

The primary analysis will be a mixed model repeated measures ANCOVA adjusting for baseline differences in dependent measures, sex and race. Missing data will be imputed by MMRM. We would also examine some variables categorically.

Assumptions for the power analysis included random assignment into one group receiving placebo and one JNJ-18038683. The cognitive battery, as the primary instrument, will be collected at baseline and at end point (8 weeks). Using repeated measure ANCOVA, the time average difference in the response variable will be compared between groups to detect treatment difference. Based on Javitt et al, 2012, we assume the mean baseline verbal learning score will be 36.2, SD 9.4 for both groups. We are assuming the placebo group will show no improvement while the treatment group will improve a mean of 5 points, a medium effect. We assume the correlation coefficient of repeated observation to be 0.5 and the covariance structure to be compound symmetry. The power calculation was conducted with alpha level of 0.05 using one-sided and two-sided tests. Full results are available upon request. With a one sided test, 33 individuals per group are required assuming 5 points improvement of the treatment group compared to the placebo for the desired power of 80% with alpha level of 0.05. We plan to recruit 36 per group to account for drop outs. In the two sided test the sample size per group is 42.

Numeric Results based on one-sided test
One-Sided Test. Null Hypothesis: D = 0. Alternative Hypothesis: D > 0 (or D < 0). Covariance Type = Compound Symmetry

Group 1 Sample Size Power(N1)	Group 2 Sample Size (N2)	Sample Allocation Ratio (R)	Time Points (M)	Difference to be Detected (D1)	Standard Deviation (Sigma)	Auto-corr. (Rho)	Alpha	Beta
0.8023533	33	1.000	2	5.000	9.400	0.500	0.050	0.19765

11.2 Data Management and Monitoring/Auditing

A database in the RedCap system will be used for data entry and will be formatted to simulate the hard copy data entry forms. Once entered into this database, the data files can be extracted into Excel or SAS project databases, which are maintained on a networked directory under the direct supervision of the PI and biostatistician. Back-ups are routinely performed to assure the preservation of the database. Data are checked for range, consistency, missing values, etc. During data analysis, combined datasets are created as needed. Data are maintained in the master system datasets using a source/derived data approach, where source datasets are maintained unmodified, while the derived datasets are modified as needed. Thus, alterations that prove to be incorrect are easily rectified. The confidentiality of all data is maintained using the HIPAA compliance standards of Northwestern University. No confidential information is posted to the web under

any circumstances. All possible efforts are made to retain only the necessary information in all cases.

Regarding de-identification of the data set: No identifiable information for any individuals (i.e. name, initials or date of birth) will be collected in the analyzable RedCap database or directly linked to study data. Individuals will be coded only with study-specific unique ID numbers.

12.0 Provisions to Monitor the Data to Ensure the Safety of Individuals

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.0 Withdrawal of Individuals*

Individuals can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Individual voluntarily withdraws from treatment (follow-up permitted);
- Individual withdraws consent (termination of treatment and follow-up);
- Individual is unable to comply with protocol requirements;
- Individual experiences toxicity that makes continuation in the protocol unsafe;
- Physician judges continuation on the study would not be in the patient's best interest;
- Individual becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).

14.0 Risks to Individuals*

The risks from the study procedures include:

In a 7 week, randomized, placebo controlled trial comparing JNJ-18038683 with placebo and escitalopram (an active comparator), a total of 6 serious adverse events were reported during the study (placebo group: spontaneous abortion and suicidal ideation; escitalopram group: spontaneous abortion, suicidal ideation, suicide attempt, and chest discomfort). A total of 10 individuals (3 in the placebo group, 4 in the JNJ-18038683 group, and 3 in the escitalopram group) were withdrawn from the study prematurely due to adverse events. Only 3 individuals receiving the 20-mg dose of JNJ 18038683 required dose reductions at any point during the study.

Adverse events that were reported in more than 5% of individuals in any treatment group included headache, nausea, nasopharyngitis, insomnia, somnolence, dyspepsia, dizziness, dry mouth, constipation, diarrhea, vomiting, back pain, upper respiratory tract infection, palpitations, and fatigue. The treatment-emergent adverse events that were reported more frequently in the JNJ 18038683 group compared with the placebo or escitalopram groups included dyspepsia, constipation, upper respiratory tract infection, and palpitations.

The clinical interview questions may result in temporary discomfort when asking the subject about a potentially difficult time in the past or the psychiatric symptoms they experience in the case of psychiatric participants. There may be temporary discomfort/ bruising at the site of venipuncture.

It is believed the potential benefits outweigh the risks for this trial.

In case of a medical emergency and risk of suicidality, the study team will follow the emergency protocol outlined in the Appendix 3.

15.0 Potential Benefits to Individuals

The possible benefits to the individuals who participate in this study are improvement in cognitive function and residual depressive symptoms, but there may be no direct benefit. Research staff could provide information from screening evaluations to the subject's clinical treatment team if requested by the subject. Findings from this study may benefit others. Participation will allow us to learn about the potential cognitive enhancing effects of JNJ-18038683 in patients with bipolar disorder, and its effect on depressive symptoms, which would inform further studies evaluating its use to treat cognitive deficits among various clinical populations.

16.0 Vulnerable Populations

This research study does involve cognitively impaired adults, as the primary endpoint is examining the effect of the study medication on the cognitive impairment associated with bipolar disorder (CIABP).

To ensure that each subject's rights and welfare are protected, we confirm the following:

The competency of patients to give informed consent will be evaluated in a multifaceted manner. The majority of patients who participate in our research are referred to us by clinicians. Prior to participating in any protocol-related procedures, and as per the standard operating procedure, research clinicians explain the nature of the protocol to the patient, the risks and benefits, and the option not to participate in research. They have been instructed by us not to refer patients they believe are incompetent or grossly disorganized. This process of assessment and explanation is then repeated by the clinician involved in the research project, often in the presence of clinical staff, and by the research assistant involved in the research project. They first do a clinical assessment to determine if the patient might be appropriate for the project in terms of its inclusion and exclusion provisions. During this clinical assessment, they do a mental status examination, which assesses the patient's memory, attention, and thinking processes. If these are impaired to the point where the person appears to be unable to understand the nature of the research project, its risks and benefits, or the option not to participate, they will not be approached to be in research. If they are not excluded for this or other reasons, e.g. patient is a risk to themselves or others, one of the subinvestigators on the study or the PI will explain the protocol, go carefully over the consent form, provide help to the patient, if needed, to review the written protocol and consent, ask question to the patient to determine their level of comprehension, and then answer all questions the patient may have about the study. This will often be done in the presence of a clinical staff member not directly connected to the research or minimally involved. This type of assessment is repeated as needed during the course of the protocol if there is a question about loss of competency, although it is expected that competency will increase rather than decrease because of the beneficial effects of the treatments. Where the research staff feels the decision as to competency is questionable, the patient will be excluded from research. In a few cases, we may ask a clinician not connected to the research to do an independent evaluation their decision will be decisive.

Individuals will be regularly evaluated for the increase of cognitive deficits. If and when increased cognitive deficits emerge, the P.I. or sub-investigator will assess for any impairments in judgment that might affect the subject's ability to judge if he or she should continue to participate. If there are any conflicts about the impairment of a given patient, the P.I, Herbert Y. Meltzer, will request Dr. John Csernansky, Chairman of the Feinberg School of Medicine Department of Psychiatry, to evaluate the patient. Dr. Csernansky will then independently determine if he believes that the patient is continuing to give consent and if continued participation is in the patient's best interest. If Dr. Csernansky determines that the patient has withdrawn consent or that continuing is not in his or her best interest, the subject will be withdrawn from continued participation and referred for appropriate follow-up treatment. If and when increased cognitive deficits emerge in a subject at the Beacon Medical Group Behavioral Health

South Bend site, the same process will take place as at the Northwestern University. If there are any conflicts about the impairment of a given patient, the P.I will ask an independent psychiatrist from the Beacon Medical Group Behavioral Health South Bend, South Bend, IN to evaluate the patient. This psychiatrist will then independently determine if he/she believes that the patient is continuing to give consent and if continued participation is in the patient's best interest.

The risk of the study is low, and are reasonable in relation to the potential benefits. Individuals cannot access alternative pharmacologic treatment for CIABP, as there is no approved treatment.

17.0 Sharing of Results with Individuals

All information will be kept confidential except such as is necessary to disclose in order to provide appropriate medical care to a study participant, in which case the participant will be notified and their healthcare provider will be contacted via phone and/or fax. If a participant is found to have severe depression, they will be referred to appropriate health care providers. If a participant's blood tests positive for Hepatitis B, local laws may require that the result be reported to local health authorities.

18.0 Setting

Participants will be identified as eligible according to diagnosis, severity of symptoms and ability to give informed consent. Staff affiliated with this research study will conduct chart reviews as allowed by mental health centers to determine eligibility based on treatment history.

All research procedures will be performed at either the Northwestern University Department of Psychiatry and Behavioral Science offices located at 680 N. Lake Shore Dr., Suite 1410, Chicago, IL 60611 or the Stone Mental Health Center, located at 446 E Ontario St, Rooms 6-344 and 6-343, Chicago, IL 60611. For the Beacon Medical Group Behavioral Health South Bend site all research procedures will be done at either the Beacon Medical Group Behavioral Health South Bend 707 N. Michigan St Suite 400 South Bend, IN 46601 or the South Bend Medical Foundation 530 N. Lafayette Blvd South Bend, IN 46601.

19.0 Resources Available

19.1 Staff and qualifications

Herbert Meltzer, MD	Principal investigator	45+ years in psychiatry clinical trials, acting as

		principal and sub-investigator.
Marko Mihailovic	Project Manager	10+ years of research experience as a rater and budget contact. Experience in management, coordination, and rating in clinical trials.
Ahmed Elmaadawi, MD	Principal Investigator Beacon Medical Group Behavioral Health South Bend	10+ years in psychiatry clinical trials, acting as principal and sub-investigator.
Suhayl Nasr, MD	Sub Investigator Beacon Medical Group Behavioral Health South Bend	15+ years in psychiatry clinical trials, acting as principal and sub-investigator.

19.2 Patients will be recruited from several clinical sites with whom we have worked closely over the last three years. Our lab has trained and certified coordinators and research assistants who will be assigned to this study as their primary responsibility. We have used a variety of cognitive batteries for schizophrenia and bipolar disorder in many studies over the last five years. Our project statistician and research staff are proficient at electronic data capture (RedCap) which we will utilize for this study.

20.0 Prior Approvals

Approval will be obtained from the Northwestern University IRB and the study sponsor, Janssen Research and Development, before commencing the research study.

21.0 Recruitment Methods

Participants aged 18-60 with bipolar disorder of at least one year duration, as established by SCID-I, will be recruited for this study. Participants will be identified as eligible according to diagnosis, severity of symptoms and ability to give informed consent. The clinical treatment providers of potentially eligible participants will be notified of the inclusion and exclusion criteria for the study, by way of written communication or regularly scheduled presentations to the providers (e.g. lunch presentations, weekly therapist meetings, etc.), and will be asked to discuss the study with potential candidates. The research staff will meet with the participants only after notification of the current provider of psychiatric

services and after the participants have expressed interest in taking part in research.

We will utilize referrals from primary care or psychiatry providers, or from participant interest and consent. We will also be recruiting individuals through the NU-SRG Recruitment Pipeline (STU00059328).

As part of the NU-SRG Recruitment Pipeline, research staff will first read individuals a verbal consent, where they can indicate if they are interested in completing a screening form and if we can hold onto their information and contact them for future research opportunities. We have prepared handouts with a flow chart to help guide candidates and clinicians to determine if candidates are preliminarily eligible for the study. We then complete a 5-10 minute screening form to determine eligibility for the study. The PI, the sub-investigator, and fully trained research staff will determine initial prescreen eligibility. The PI will personally review and approve all enrollees prior to randomization.

22.0 Local Number of Individuals

After screening for eligibility and providing written informed consent, 60 stable outpatients, who may have mild-moderate depressive symptoms, will be randomized to receive adjunctive treatment with either JNJ-18038683 or placebo.

We propose to study a total of 60 randomized participants, 30 receiving JNJ-18038683 and 30 randomized to placebo.

23.0 Confidentiality

All data that will be stored on sites and will be maintained in locked cabinets (double lock rule applies). Blood specimens will be processed locally at Northwestern Memorial Hospital and South Bend Medical Foundation. Only NU-IRB approved members of the study team will have access to the study data. De-identified data will be kept separately from the identified data. De-identifiable data will be entered into a RedCap data base that serves as an Electronic Data Capture (EDC) system,

24.0 Provisions to Protect the Privacy Interests of Individuals

Participants will be reminded whenever appropriate that they are at liberty to opt out of answering any questions or undergoing any procedures with which they are not comfortable, up to and including their right to rescind their participation in the study without any penalty unto them.

Participants must sign an authorization for release of information before any sources of information can be contacted about the participant.

25.0 Compensation for Research-Related Injury

25.1 If the research involves more than Minimal Risk to individuals, describe the available compensation in the event of research-related injury.

25.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

26.0 Economic Burden to Individuals

Participants may incur costs related to transportation by participating in this study, and they will be reimbursed for part or all of such incurred expenses.

Individuals will be compensated at the rate of $40/visit for their time and effort. The total amount for visit compensation will be prorated based on subject's participation. Up to $20 per visit will also be provided to cover individuals' transportation and parking expenses. For any visit lasting over 4 hours $10 will be provided to cover subject's lunch costs.

27.0 Consent Process

The informed consent form will typically first be discussed with a potential participant over telephone, and after the participant has considered their ability to participate in the study, will again formally be reviewed with the participant during an in-person screening visit at the Northwestern University Department of Psychiatry and Behavioral Science offices or at the Beacon Medical Group Behavioral Health South Bend. Any time that there is a change in the protocol or the informed consent form, the revised consent form will again be reviewed with and signed by the participant. Individuals obtaining consent will follow 'SOP: Informed Consent Process for Research (HRP-090).'

No non-English speaking participants, minors, cognitively impaired adults, or adults unable to provide consent will be considered for participation in this study, nor will any waivers or alterations of the consent process be applied for.

28.0 Process to Document Consent in Writing

Individuals documenting the consent in writing will follow 'SOP: Written Documentation of Consent (HRP-091).'

29.0 Drugs or Devices

JNJ-18038683 will be provided by Janssen Research and Development, the makers of JNJ-18038683, and will provide a detailed Certificate of Analysis attesting to the contents of the product.

The investigational product has been assigned the number JNJ-18038683-ADC. The suffix ADC denotes the citrate salt form and JNJ-18038683-ADC is referred

to as JNJ-18038683 unless stated otherwise. Alternatively, the number RWJ-800054 may also be used to denote the citrate salt form.

The full International Union of Pure and Applied Chemistry (IUPAC) chemical name is 3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-1-(phenylmethyl)pyrazolo[3,4-d]azepine 2-hydroxy-1,2,3-propanetricarboxylate (1:1). JNJ-18038683 has been assigned the Chemical Abstract Service (CAS) registry number 851376-05-1.

An oral solid dosage formulation has been manufactured as tablets containing 10 mg of JNJ-18038683, lactose monohydrate, croscarmellose sodium, povidone, silicified microcrystalline cellulose, and magnesium stearate. The placebo formulation will be supplied as matching tablets. Detailed instructions for storage conditions and oral dose administration will accompany the clinical drug supplies to the clinical study sites.

The target dosage will be 20 mg/day, or 2 tablets of 10 mg once per day. This will preserve the blind, as the placebo comparator will be also given as 2 tablets once per day. Individuals will receive 10 mg/day for the first week, and 20 mg from weeks 2-7 with a provision for a single, downward, dose adjustment.

Study clinicians will be responsible for dispensing JNJ-18038683 at our research office. An unblinded study drug manager will receive and label and distribute the product for dispensing during the study.

At the baseline and end of study visits, measures of safety and effectiveness will be administered and individuals will be evaluated for response and side effects to the treatment. To assess adherence to dosing of the agent, the study medication will be returned and counted.

Study drugs sent by the sponsor to the study site will be stored in a locked cabinet and be handled only by the study coordinator, who will also maintain drug accountability logs and drug destruction/return logs that will be verified by the site monitor to ensure that study drugs have only been used on individuals and only by authorized investigators.

Study Drug/Study Device: JNJ-18038683

IND/IDE Number: 126601

IND/IDE Holder Name: Herbert Meltzer, MD

31.0 References

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Appendix 1

Schedule of Assessments:

Study Day	Screen	1	7	14	21	28	35	42	49	56	84
Event/Assessment					**PC**		**PC**		**PC**		**PC**
Informed Consent	X										
Medical History & Demographics	X										
Physical Examination	X										
Electrocardiogram	X					X				X	
Vital Signs	X	X	X	X		X		X		X	
Clinical Safety Laboratory Tests	X					X				X	
Serum Pregnancy Test	X										
Urine Pregnancy Test		X								X	
Urine Drug Screen	X										
Inclusion/Exclusion Criteria	X										
SCID-I	X										
Screening neurocognitive assessments	X										
Montgomery Asberg Depression Rating Scale		X				X				X	
SLOF		X								X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
AIMS		X				X				X	
Neurocognitive battery		X								X	
CGI-BP		X				X				X	
Young Mania Rating Scale		X				X				X	
Assessment of Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Assessment of Adverse Events	X	X	X	X	X	X	X	X	X	X	X

Appendix 2: Prohibited medications:

CYP2D6 Inhibitors
Bupropion
Celecoxib
Cinacalcet
Chloroquine
Chlorpheniramine
Clemastine
Clomipramine
Diphenhydramine
Duloxetine
Fluoxetine
Halofantrine
Hydroxyzine
Methadone
Moclobemide
Paroxetine
Pyrilamine
Quinidine
Terbinafine
Tripelennamine
Aripiprazole

Moderate to potent CYP2C19 inhibitors
Fluconazole
Fluvoxamine
Ticlopidine
Esomeprazole
Moclobemide
Omeprazole
Voriconazole

Atypical Antipsychotics
Clozapine

Major substrates and inhibitors for CYP2D6 [38]

Specific drugs as substrates
Alprenol
Amiflamine
Aprindine
Atenolol
Bufuralol
Bupranolol
Chlorpropamide
Clomipramine
Codeine
Debrisoquine
Desimipramine
Desmethylcitalopram
Dextromethorphan
Dihydrocodeine
Encainide
Ethylmorphine
Flunarizine
Fluperlapine
Guanoxan
Haloperidol
Hydrocodone
Imipramine
Indoramin
Maprotiline
Methoxyamphetamine
Methoxyphenamine
Metiamide
Metoprolol
Mexiletine

Inhibitors, drugs
Chinidin
Fluoxetin
Levomepromazine
Lobelin
Methadone
Quinidine
Trifluperidol

Inhibitors, alkaloids
Ajmalicine
Berberine
Coniine
Ergotamine
Gramine
Harmaline
Sempervirine
Vincamine
Vinblastine

Nortriptyline
Ondansetron
Otycodone
Perhexiline
Perphenaxine
Phenacetin
Phenformin
Propafenone
Propranolol
Quinidine
Thioridazine
Timolol
Tomoxetine
Tropisetron
Zuclopenthixol

Appendix 3: Emergency protocol:
This procedure will be followed whenever the research staff is in contact with the study participants either in person or via phone

Emergency procedures:
If there is an apparent imminent medical risk, call 911. A research team member must watch on the subject until Police/Ambulance arrives.

If there is an imminent medical risk, the other immediate safety procedures to be followed by clinical research staff.

If there is no apparent imminent risk, the following protocol will be followed:

- Alert the Principal Investigator (PI) and/or Study Doctor about the problem (provide with demographics and relevant medical information such as suicidal, homicidal ideation/intent, diagnosis, medical condition, etc.)
- Based on the clinical judgment of PI and/or Study Doctor, 911 may be called at any time during this procedure or appropriate care will provided at the site.
- Alert the Research Manager (provide with relevant information)
- Contact the primary treating psychiatrist.
- Pending response (if recommended to proceed to the Emergency Department (ED), discuss the issue with all relevant research staff and participant as well as the participant's family members and/or caregivers if appropriate.
- Call 911
    - In the case of an involuntary hospitalization/ED evaluation - call Police – a research team member should go with police since "Petition" is required.
    - In the case of a voluntary hospitalization/ED evaluation - call Ambulance to escort the patient.
- In the case of suicidal ideation/intent, a research team member must watch on the subject until Police/Security/Ambulance arrives.
- Contact the building security and inform them that Police and/or Ambulance was contacted.
- A Clinical Research Team Member needs to provide documentation from the investigator to give to the police/security regarding the investigator recommendation.
- A Clinical Research Team Member calls ED to alert that patient is on the way and to provide with all necessary information.
- A Clinical Research Team Member follows up with crisis team/on call resident to give information about the patient.

- A Clinical Research Team Member documents all activities for the study file and for correspondence with clinicians/, sponsor, IRB and Janssen Research and Development, LLC.