A multi-center, randomized, controlled trial of brexpiprazole for the treatment of co-occurring schizophrenia and substance use disorder

Document date: Version 6.2 – January 7th, 2022

NCT Number: NCT03526354

PRINCIPAL INVESTIGATOR: **XIAODUO FAN, MD**

Funding Provided by: **Otsuka Pharmaceuticals**

TABLE OF CONTENTS

Synopsis

Protocol Number:	
Title:	A multi-center, randomized, controlled trial of brexpiprazole for the treatment of co-occurring schizophrenia and substance use disorder
Design:	The proposed study is a 4-site, 12-week, feasibility, "proof of concept" investigation of patients who have co-occurring diagnoses of schizophrenia and current substance use disorder (alcohol, cocaine, heroin, or cannabis).
Primary Objectives:	The primary objectives of this study: 1) examine the effect of brexpiprazole treatment on the number of days of substance use in the past week as measured by the Timeline Follow-Back (TLFB) assessment; 2) examine the effect of brexpiprazole treatment on substance craving using 100-mm visual analogue scale (VAS).
Secondary Objectives	The secondary objectives are to examine the effect of brexpiprazole treatment on: 1) the dollar amount spent on substances in the past week; 2) the psychiatric symptoms as measured by various clinical rating scales; 2) quality of life.
Enrollment:	50 subjects total
Clinical Sites:	4 US sites
Timeline	Initial enrollment (expected): February 15, 2018 Last enrollment (expected): November 20, 2023 Last anticipated follow-up contact: February 29, 2024
Patient Population:	Men and women, 18-65 (inclusive) years of age Age 18-65 years old. Meets the DSM-5 criteria for diagnoses of schizophrenia or schizoaffective disorder and substance use disorder (alcohol,

	cocaine, heroin, or cannabis) based on the Mini International Neuropsychiatric Interview (MINI).
Primary and Secondary Outcomes:	The number of days of substance use in the past week as measured by the Timeline Follow-Back (TLFB). Substance craving using 100-mm visual analogue scale (VAS). Psychiatric symptoms will be assessed using: 1) The Positive and Negative Symptoms Scale (PANSS), 2) the Schedule for the Assessment of Negative Symptoms (SANS), 3) the Calgary Depression Rating Scale (CDRS), and 4) the Clinical Global Impression Scale (CGI); Quality of life as measured by the Heinrichs Carpenter Quality of Life Scale (QOL).
Inclusion Criteria:	1) Age 18-65 years old 2) Meets the DSM-5 criteria for diagnoses of schizophrenia or schizoaffective disorder and substance use disorder (alcohol, cocaine, heroin, or cannabis) based on the Mini International Neuropsychiatric Interview (MINI). 3) Uses substance on at least 4 of the past 30 days prior to randomization with at least one use in the week prior to randomization for one of substances (cocaine, heroin, cannabis or alcohol) assessed by the TLFB interview 4) Stable dose of antipsychotic agent for at least one month 5) Well established compliance with outpatient medications 6) Female subjects of child-bearing potential are required to practice appropriate birth control methods during the study.

Exclusion Criteria:	1) Psychiatrically unstable 2) Currently meets DSM-5 criteria for any substance use disorder other than caffeine, nicotine, alcohol, cocaine, heroin and cannabis 3) Significant, unstable medical conditions including severe cardiovascular, hepatic, renal or other medical diseases 4) History of a seizure disorder 5) Pregnancy or breastfeeding 6) Currently on aripiprazole or cariprazine 7) Currently on medications to treat substance use (disulfiram, naltrexone, acamprosate,methadone, buprenorphine, varenicline or bupropion)
Statistical Methodology	Intent-to-treat analysis and a mixed model approach will be conducted to estimate the pragmatic effects of brexpiprazole treatment on the number of days of substance use in the past week, substance craving, psychiatric symptoms and quality of life. Polynomial time trends (e.g., slopes) will be used to fit the population mean response curve for the control group. Group-by-time interactions will be modeled as a function of time to fit between-group effects. Subject-specific parameters will be estimated to model individual subject deviations from the group mean. Baseline measures of substance use and clinical symptoms will also be included in the model as covariates.

A. INTRODUCTION AND BACKGROUND

The lifetime prevalence of substance use disorders in patients with schizophrenia has been reported ranging from 10 to 60% (1). The lifetime prevalence of Alcohol use disorder is at least three times more common in patients with schizophrenia than in the general population. The co-occurrence of cannabis use disorder happens in 13-42% of patients with schizophrenia. Co-occurring substance use is associated with increased relapse and re-hospitalization rates, non-compliance with treatment, an increased risk for violence, and poorer global functioning (2, 3). Clearly, substance use adds greatly to the financial costs and emotional toll that schizophrenia places on patients, families, and the entire mental health system.

Treatment challenges for schizophrenia and co-occurring substance use

Patients who present with schizophrenia and co-occurring substance abuse can be difficult to manage in the outpatient setting. The lack of integrated care to address both psychotic symptoms and substance problems and the poor treatment compliance are two major challenges. Poor treatment compliance is contributed by the active positive and negative symptoms and ongoing use of substance. In spite of the high association between the two conditions, there is a surprising paucity of studies to explore optimal treatment and outcome for this patient population. Most antipsychotic agents are of limited value in controlling substance use in these dual diagnosis patients. Studies have suggested that clozapine decreases alcohol and cannabis use in dual diagnosis patients with schizophrenia. However, significant side effects produced by clozapine severely limit its clinical use (4, 5).

The promise of Dopamine D2 receptor partial agonists

Recent research has suggested that the dopamine D_2 receptor partial agonists, such as aripiprazole, decrease drug addiction in several animal models (6, 7). Studies have also reported that aripiprazole can reduce substance craving and use in patients with schizophrenia or bipolar disorder (8). It has been suggested that aripiprazole can lessen alcohol and substance use in dual diagnosis patients in part because of its mechanism of action that includes release of dopamine in the prefrontal cortex which helps normalize dysfunctional brain reward circuits (BRC) that may underlie the co-occurring alcohol and substance use in patients with schizophrenia (9).

Brexpiprazole is a newly approved dopamine D_2 receptor partial agonist for schizophrenia treatment. It shows partial agonism with lower intrinsic activity at

the D_2 receptor and stronger antagonism at the 5-HT_{2A} receptor than aripiprazole (10). We hypothesize that brexpiprazole, similar as aripiprazole, can decrease the level of craving and reduce the use of substance in patients with schizophrenia; further, brexpiprazole may be even more efficacious than aripiprazole in reducing substance use given its relatively lower potential to induce D_2 partial agonist-mediated activating adverse effects such as restlessness, insomnia, and nausea (11), which are common substance withdrawal symptoms.

B. RATIONALE AND STUDY DESIGN

The proposed study is a 4-site, 12-week, novel, feasibility, “proof of concept” investigation of patients who have co-occurring diagnoses of schizophrenia and current substance use disorder (alcohol, cocaine, heroin, or cannabis). Fifty patients not treated with aripiprazole or cariprazine (the other two dopamine receptor partial agonists) at the time of consent will be randomly assigned to switch to brexpiprazole (the brexpiprazole group) or remain on the same antipsychotic treatment (the control group).

C. STUDY OBJECTIVES

The primary objectives of the study include:
1) examine the effect of brexpiprazole treatment on the number of days of substance use in the past week as measured by the Timeline Follow-Back (TLFB) assessment;
2) examine the effect of brexpiprazole treatment on substance craving using 100-mm visual analogue scale (VAS).

The secondary objectives are to examine the effect of brexpiprazole treatment on:

1) the dollar amount spent on substances in the past week;
2) the psychiatric symptoms as measured by various clinical rating scales;
3) quality of life.

Additional objectives of this study include collection of additional safety data on brexpiprazole using safety parameters (ECG, metabolic labs, vital signs, suicidality, EPS, side effects measured by the SAFTEE) throughout the study

D. STUDY POPULATION

The study will be conducted at 4 sites in the US. We expect to enroll 50 subjects across 4 sites. We anticipate a 20% discontinuation for this study. Hence we will randomize 50 subjects so we will have 40 subjects completing the study.

Eligibility Criteria

Inclusion criteria:
Each subject must meet all study inclusion criteria prior to randomization.

1) Age 18-65 years old
2) Meets the DSM-5 criteria for diagnoses of schizophrenia or schizoaffective disorder and substance use disorder (alcohol, cocaine, heroin, or cannabis) based on the Mini International Neuropsychiatric Interview (MINI).
3) Uses substance on at least 4 of the previous 30 days prior to randomization with at least one use in the week prior to randomization for one of the substances (cocaine, heroin, marijuana or alcohol) as assessed by the TLFB interview
4) Stable dose of antipsychotic agent for at least one month
5) Well established compliance with outpatient medications
6) Female subjects of child-bearing potential are required to practice appropriate birth control methods during the study.
7) Male subjects who are sexually active must agree to use appropriate birth control measure to avoid partner pregnancy

Exclusion criteria:
Each subject must not have the following exclusion criteria prior to randomization in the study.

1) Psychiatrically unstable
2) Currently meets DSM-5 criteria for any substance use disorder other than caffeine, nicotine, alcohol, cocaine, heroin and cannabis.
3) Significant, unstable medical conditions including severe cardiovascular, hepatic, renal or other medical diseases
4) History of a seizure disorder
5) Pregnancy or breastfeeding
6) Currently on aripiprazole or cariprazine
7) Currently on medications to treat substance use (disulfiram, naltrexone, acamprosate, methadone, buprenorphine, varenicline or bupropion)
8) Patients previously exposed to brexpiprazole

Exclusionary Lab values:

Comprehensive Metabolic Panel	
Sodium	<1.1 times the lower limit or >1.1 times upper limit of the reference range

Potassium	<1.1 times the lower limit or >1.1 times upper limit of the reference range
Blood Urea Nitrogen (BUN)	>1.3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
Aspartate amino transferase (AST)	>3 times upper limit of the reference range
Alanine amino transferase (ALT)	>3 times upper limit of the reference range
Glycated Hemoglobin (HbA1c)	Patients with a value > 9.0% (at screening only)
eGFR	< 35 ml/min

E. SCHEDULE OF EVENTS AND STUDY ASSESSMENTS

Table 1. Schedule of Events

Procedure	Visit	Screening	Visit 1 (baseline)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13/EOT	Early Termination (ET)
	Study Week		**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6 or ET at week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Any visit other than at week 6**
Medical History		X														
Physical Exam		X														
MINI		X														
Pregnancy Test (Females only)		X														
Post-Screening Pregnancy Checklist			X			X			X			X				
ECG		X							X						X	X
Labs (CMP, Lipid Panel, CBC, Hs-CRP, IL6, TNFα)		X							X						X	X (only CMP, Lipid panel, and CBC)
Lab (HbA1C)[4]		X														
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X	X													
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference			X						X						X	
TLFB[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fagerstrom Test	X							X						X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PANSS		X						X						X	
SANS		X						X						X	
CDRS		X						X						X	
CGI-S and CGI-I[2]		X						X						X	
CSSRS	X	X						X						X	X
QOL		X						X						X	
EPS Scales (BAS, SAS, AIMS)		X						X						X	
Drug dispensing		X	X	X		X		X		X		X			
Supportive Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	

1- TLFB at screening will be completed for the past 30 days. All other visits the TLFB will collect information for the past week.
2- CGI-I will not be administered at baseline. Only CGI-S is administered at baseline.
3- EOT – end of treatment
4- Lab (HbA1C) will only be performed at the screening visit
5- If ET falls on week 6, the visit should follow regular week 6 protocol. If ET falls on any other visit, follow ET protocol

Informed Consent Process: All subjects will sign IRB approved informed consent form (ICF) prior to starting any study related screening procedures. The written informed consent will be obtained by authorized study personnel. The authorized study staff will explain the study objectives, risks and benefits and overview of the study procedures to all subjects as part of the consent process.

Eligibility Review: An eligibility review will be conducted by the investigator at each site as per the inclusion exclusion criteria listed in section D of the protocol. All subject eligibility criteria will be reviewed by UMass designee prior to subject randomization.

Demographics and Medical/Psychiatric History: Subject's demographics, medical and psychiatric history will be collected as part of the screening process. All patient medical and psychiatric history will be reviewed by the investigator.

Mini International Neuropsychiatric Interview (MINI v7.0): The MINI 7.0 is used for evaluation of major Axis I psychiatric disorders in DSM-5™.It is a short clinician-administered structured diagnostic interview with an administration of around 20 minutes. The MINI will be administered by the investigator.

Concomitant Medication Review: All medication (prescription or non-prescription, including vitamin and herbal supplements) taken by subject 30 days prior to screening must be recorded and reviewed. At each visit the concomitant medications will be recorded and reviewed by investigator or their designee as per the concomitant medication sheet (appendix)

Vital Signs: Vital signs will be assessed by designated study staff after the subject is seated for 5 minutes. Vital sign assessment will include sitting and standing systolic and diastolic blood pressure, heart rate (sitting and standing) and oral temperature. Vital signs must be assessed as per the schedule of events (SOE) and reviewed by the study MD. Effort should be made to consistently use the same arm to measure blood pressure throughout the study. Any clinically significant vital signs will be recorded as an adverse event and documented in the source document and eCRF.

Physical Examination: A complete physical exam will be conducted at screening by the PI or a medically qualified designee. The examination should include assessment of head, neck, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, cardiovascular and nervous systems.

Anthropometric measurements: Height and weight will be recorded. Height is recorded at screening visit only. Weight (kg) will be recorded at every visit. BMI will be calculated at all visits and is defined as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference will be measured at baseline, week 6 and week 12.

12- Lead Electrocardiogram (ECG): A 12-lead ECG will be administered after the patient is supine for 5 minutes. ECG will be administered as per the schedule of events. The ECG will be reviewed by PI or medically qualified sub-investigator for any abnormalities. The ECGs findings will be marked as normal, abnormal-not clinically significant or abnormal-clinically significant by PI or medically qualified sub-investigator.
Any clinically significant change noted from screening or if an ECG is considered abnormal and clinically significant, it will be reported as an AE and will be appropriately recorded in both the source documents and the eCRF.

Laboratory Procedures: Most of the lab procedures will be done at the site. All blood work will be done as fasting.

Routine lab panels done at site include: Hematology (CBC with diff), comprehensive metabolic panel (CMP) and lipid panel. These labs will be assessed at screening, week 6 and week 12. Routine lab panels will be collected for subjects who are early terminated. Additionally, an HbA1c test will be conducted at screening only. Approximately four tablespoons of blood will be taken at each blood draw.

Lab samples for Hs-CRP, IL6 and TNF -alpha will be collected by sites and stored at -80F. It will be batch shipped to UMass every 6 months. These will be analyzed at UMass Memorial labs. CRP, IL-6 and TNF-α are well established inflammatory markers that are associated with both psychopathology and metabolic side effects in patients with schizophrenia. We will analyze how brexpiprazole treatment might affect these inflammatory markers.

Routine Lab Assessments at site:

Hematology (CBC)	**Comprehensive metabolic panel**	**Lipid Panel**
Hematocrit Hemoglobin Platelets	Alanine transferase (ALT) Albumin Total protein	Total cholesterol Chol, HDL Triglyceride Chol, LDL

Red blood cell count Total and differential (absolute) white blood cell count	Alkaline phosphatase (ALK-P) Aspartate transferase (AST) Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Potassium Sodium Chloride Estimated glomerular glomerular filtration rate (eGFR)	Chol, VLDL Cholesterol/DL ratio

Future Testing: Blood samples will be collected at screening, week 6 and week 12 for use in future research related to schizophrenia. All samples will be labelled with a study ID. Only members of the research team will be able to derive an individual's identity from their study ID code. The key to the code is stored on secure server and can only be accessed through password-protected computer Sub-sites will store these at -80F and batch ship them to the UMass Psychotic Disorders Research Program at UMass Medical School for storage and future extraction/genotyping. The lead site will store all samples indefinitely.

Pregnancy Tests: A urine dip stick pregnancy tests will be administered to all women at screening. The pregnancy test can be repeated at any time during the study as per PI discretion. All subjects must test negative for pregnancy tests to be eligible for the study.

Urine Drug Tests: All subjects must undergo urine drug tests for a panel of substances at every study visit. The urine drug test will be completed prior to administering the timeline follow-back (TLFB).
The urine drug screen will include opioids, cocaine, methamphetamines, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine.

Supportive Counseling: Qualified staff will provide supportive counseling to study subjects at weekly visits. Brief supportive counseling sessions about substance use will be provided as part of study visits. The content and structure is adapted

from the Individual Resiliency Training (IRT) manual that was originally developed for the RAISE (Research to identify, optimize and personalize early treatment for people affected by schizophrenia) study (Mueser et al., Psychiatric Services 2015; 66:680-690). Counseling will be provided to all subjects. Counseling is not manualized and no fidelity check is planned. Counseling will focus on:
1) substance abuse counseling to encourage a reduction in or abstinence from alcohol consumption;
2) Medication management counseling to encourage compliance with the treatment.

Efficacy Assessments

Timeline Follow-back (TLFB): Substance use will be recorded using the timeline follow-back method at every study visit. At screening visit, TLFB will assess substance use and dollar amount spent on substances for the past 30 days. All other visits will collect substance use data and dollar amount spent in the past week or for the period between the last visit and the current visit. The subject's drug screen results will be conveyed to the subject prior to administration of the TLFB. If the subject's self-report is at odds with the drug screen results, then the subject's report will not be challenged. All reported data from the subject and drug test results will be collected and used in exploratory analyses

Visual Analog Scale (VAS): The VAS will be used to assess craving for substance use as per the schedule of events and administered as per the schedule of events. The VAS is a horizontal line with a unipolar scale, anchored on the right side with
"No desire at all" (marked with a "0") and on the left side with "Worst imaginable desire" (marked with a "100" with a line connecting the two ends. Subjects will mark the appropriate point to indicate where their "desire for substance" falls on this line.

Fagerstrom Test: The Fagerstrom Test for Nicotine Dependence will be used to assess smoking status. Data on subjects will be collected using the Fagerstrom test as per the schedule of events.

Positive and Negative Syndrome Scale (PANSS): PANSS is a measure used to assess symptom severity in patients with schizophrenia. It consists of three sections: Positive scale has 7 items, Negative scale has 7 items and General

Psychopathology has 16 items. Each item (symptom) will be scored on a 7-point scale with higher scores representing increasing levels of psychopathology: 1) Absent, 2) Minimal, 3) Mild, 4) Moderate, 5) Moderate severe, 6) Severe, and 7) Extreme. The PANSS will be administered by a designated study staff at time points specified in the schedule of events.

Schedule of Assessment of Negative Symptoms (SANS): SANS is a 24-item scale used to assess negative symptoms based on observation and a structured interview in patients with schizophrenia. Designated study staff will administer the SANS at baseline, week 6 and week 12.

Calgary Depression Rating Scale (CDRS): The Calgary Depression Rating Scale is used to depression symptoms in subjects. The PI or a designated staff will administer the CDRS at baseline, week 6 and week 12.

Clinical Global Impression – Severity and Clinical Global Impressions – Improvement Scales (CGI-S and CGI-I): The CGI-S and CGI-I are observer rated scales. The CGI-S measures illness severity on a 7-point Likert scale 1) Normal, not at all ill, 2) Borderline mentally ill, 3) Mildly ill, 4) Moderately ill, 5) Markedly ill, 6) Severely ill, and 7) Among the most extremely ill patient. The CGI-I is used to measure improvement in illness and also uses a 7 point Likert scale: 1) Very much improved, 2) Much improved, 3) Minimally improved, 4) No change 5) Minimally worse, 6) Much worse, 7) Very much worse. The PI or a designated study staff will administer this at time points as per the schedule of events.

Heinrichs Carpenter Quality of Life Scale (QOL): The QOL is a 21-item scale providing information on symptoms and functioning in patients with schizophrenia. A trained designated study staff will administer the QLS at baseline, week 6 and week 12.

Safety Assessments

Extra Pyramidal Symptoms (EPS) Scales: The PI or a designee will complete the following EPS scales – The Abnormal Movement Scale (AIMS), Barnes Akathasia Scale (BAS) and the Simpson Angus Scale (SAS). These movement scales will be assessed at baseline, week 6 and week 12.

Columbia Suicide Severity Rating Scale (CSSRS): The PI or a designee will administer the C-SSRS. The C-SSRS will be administered at screening,

baseline, week 6 and week 12. The C-SSRS should be administered by a clinician trained to assess and manage suicidal ideation and behavior.

Adverse Events (AE): Adverse events will be monitored at each weekly visit. The PI or the sub-investigator will review adverse events at every study visit. AE information is collected and recorded starting on the day the consent is signed until the end of an individual's participation in the study.

F. STUDY VISIT PROCEDURES AND SCHEDULE

The proposed study is a 4-site, 12-week, novel, feasibility, "proof of concept" investigation of patients who have co-occurring diagnoses of schizophrenia and current substance use disorder (alcohol, cocaine, heroin, or cannabis). Fifty patients not treated with aripiprazole or cariprazine at the time of consent will be randomly assigned to switch to brexpiprazole (the brexpiprazole group) or remain on the same antipsychotic treatment (the control group).

Informed consent will be obtained prior to the screening visit and any study procedures.

Screening Visit: Screening visit assessments includes: Fasting blood samples for lipid profile, comprehensive metabolic profile, CBC, hs-CRP, IL-6 and TNF-α will be obtained at the screening visit. Potential subjects will undergo a diagnostic evaluation. Psychiatric diagnosis will be determined using the Mini International Neuropsychiatric Interview (MINI).A medical evaluation, including weight, height, vital signs, a physical examination, and review of systems will be performed. A urine pregnancy test will be performed on all women of childbearing potential. The subjects will be given an appointment card for their next visit which will also provide a reminder for the use of appropriate birth control. In addition, a urine drug screen, and a 12-lead EKG will be performed. A 30-day timeline follow-back will be administered at screening visit to assess current substance use and Fagerstrom test will assess smoking status.

Following the screening visit and prior to baseline visit, the subject's primary care provider and/or psychiatrist will be notified of their participation in the study in order to adequately screen subjects, ensure that only eligible subjects are enrolled, and minimize subject risk.

All screening procedures will be completed and reviewed by PI for eligibility criteria prior to randomization/baseline visit.

Randomization: After completion of all screening assessments, all patient eligibility screening documents will be sent to UMass for review and eligibility confirmation. Once a patient is deemed eligible, a randomization ID and a randomization condition (brexpiprazole versus control) for the subject will be generated. The randomization condition will be accessible to the site and their pharmacy and will be used to prepare the corresponding study treatment. Once a subject has been assigned a randomization ID, they will be identified in the CRF by this randomization ID for the duration of their study participation.

Baseline Visit: Subjects will be randomly assigned to switch to brexpiprazole (brexpiprazole group) or remain on the same antipsychotic medication (control group).

Study intervention**:** Brexpiprazole switch: For the brexpiprazole group, an overlap and taper switch method will be used. The current antipsychotic medication will be tapered following standard clinical practice and discontinued over a time period of 6 weeks. Brexpiprazole will be started at 1mg/day for 4 days, and 2mg/day for 3 days, and then titrate by up to 1mg/day increase every 3 days to reach 4mg/day, or as much and as fast as the participant can tolerate. Participants will stay on 4mg/day or the highest tolerable dose until the end of the study.

Medication adherence will be measured via pill counts at weekly visits. The study staff will discuss pill count data with participants to emphasize the need to take the study medication.

If participants cannot tolerate brexpiprazole after randomization, it will be stopped, though the participant may continue to be followed on another treatment (ideally their pre-study antipsychotic medication) for the remaining weeks of the study. The subject will then continue the rest of the study on their previous antipsychotic medication.

The following assessments will be completed at baseline visit:

1) Anthropometric measures (weight, waist circumference and height at screening to be used) and Vital signs
2) Weekly TLFB
3) Drug screen
4) Post-Screening Pregnancy Checklist
5) AE review
6) PANSS, SANS, QLS, CGI-S
7) C-SSRS, EPS scales, CDRS
8) Supportive counseling

Week 6 and week 12 visits: The following assessments will be done at week 6 and 12.

1) Anthropometric measures (weight, waist circumference) and Vital signs
2) Weekly TLFB
3) Drug screen
4) Post-Screening Pregnancy Checklist (Week 6 only)
5) AE review
6) PANSS, SANS, QLS, CGI-S
7) C-SSRS, EPS scales, CDRS
8) Supportive counseling
9) ECG
10) Labs (CMP, CBC, lipid panel)
11) Labs – hs-CRP, IL-6 and TNF-alpha collected and stored at -80F
12) Fagerstrom test

Week 2, 3,4,5,7,8,9,10,11 visits: These visits may be completed virtually through a secured platform depending on the most current COVID situation. During the virtual routine follow up visits, vital signs and urine drug screen will be unable to be collected; but all subjects who go through the switch will have demonstrated no clinically significant changes in vitals, ECG, or lab results in prior long visits. The following assessments will be administered at these weekly visits:

1) Vital signs and anthropometric measures (weight)
2) Urine drug screen
3) Post-Screening Pregnancy Checklist (Week 3 and 9 only)
4) TLFB
5) AE review
6) Supportive counseling

End of Study / Discontinuation of Study Medication – When a participant who is randomized to brexpiprazole completes Visit 12 (or sooner for those discontinuing study medication), he or she will no longer receive medications through the study. There will need to be a discussion with the participant and his/her treatment provider as to whether or not the participant will continue on the study medication after the subject's study participation is over. For participants finishing the study at Visit 12, this discussion should occur about three weeks prior to the final visit. If the participant will continue on the study medication, the treatment provider can begin to prescribe the medications following standard clinical practice. The monitoring and management of symptoms, therapeutic response and medication side effects will be the responsibility of the treatment provider.

Subjects who do not wish to continue on the study medication after the end of study, the treatment provider can begin to manage a cross titration off the study medication and on to either the antipsychotic medication prior to the study or a new antipsychotic medication following standard clinical practice. The monitoring and management of symptoms, therapeutic response and medication side effects will be the responsibility of the treatment provider.

Withdrawal of Subjects

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The investigator must withdraw any subject from the study who requests to be withdrawn or fits the criteria below:

1) If subject meet any exclusion criteria after enrollment.

2) If subjects have laboratory results that meet the exclusionary criteria range during the study, the subject will have his/her labs repeated before being withdrawn from the study.

3) Subjects will be withdrawn from the study is there is an increase in their PANSS total score greater than or equal to 20 compared to their baseline total score at any point during the study.

4) Female subjects may be terminated from the study if they become pregnant at any time while participating in the study.

5) If at any time the study sponsor or research personnel at UMass decide to terminate the study, subjects' consent will be withdrawn involuntarily.

Early Termination Visit

If the subject is terminated from the study on what would be their week 6 visit, they will complete all the assessments that are required in a regular week 6 visit. If the subject is terminated from the study at any other point, only safety procedures will be performed (listed below).

1. Vital signs and anthropometric measures (weight)
2. Urine drug screen
3. TLFB
4. AE review
5. Safety labs (CMP, CBC, lipid panel)
6. ECG
7. CSSRS

G. TREATMENT OF SUBJECTS

Study Drug Dose and Administration

The study drug brexpiprazole (Rexulti) will be administered orally. Subjects will be randomly assigned to either switch to brexpiprazole or remain on the same antipsychotic medication (treatment as usual). Subjects randomized to brexiprazole treatment will be titrated as per section F (study intervention). Study participants randomized to brexpiprazole treatment will be titrated to 4mg/day or the highest tolerable dose as per the study MD's clinical judgement until the end of the study. Dose de-escalation due to tolerability will be allowed in the study. If subjects recover, the dose can be increased to the 4mg or the highest tolerable dose as per the MD's clinical judgement. Patients who are unable to tolerate a minimum dose of 1 mg will be withdrawn from the study

Study Drug

Commercially available brexpiprazole will be provided directly to all sites by Otsuka Pharmaceuticals. Study drug will be provided as 1mg and 2mg tablets. Subjects will take medications as dispensed by their site's Investigational drug pharmacy.

Storage and Drug Accountability

The study drug will be stored as per the drug insert. The sites are required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Prohibited Medications

Currently on the following antipsychotics

- Aripiprazole
- Cariprazine

Currently on medications to treat substance use such as:

- Disulfiram,
- Naltrexone,
- Acamprosate,
- Methadone,
- Buprenorphine,
- Varenicline
- Bupropion

Special Consideration for Concomitant Medications with Brexpiprazole

Medications	Intervention

Strong CYP3A4 inhibitors *Examples:* itraconazole, clarithromycin, ketoconazole	With concomitant use of brexpiprazole with a strong CYP3A4 inhibitor, reduce the brexpiprazole dosage and administration [see drug insert dosage and administration (2.5)]
Strong CYP2D6 inhibitors Examples: paroxetine, fluoxetine, quinidine	With concomitant use of brexpiprazole with a strong CYP2D6 inhibitor, reduce brexpiprazole dosage [see drug insert dosage and administration (2.5)]
Both CYP3A4 inhibitors and CYP2D6 inhibitors *Examples:* 1) itraconazole+quinidine 2) fluconazole+paroxetine 3) itraconazole+duloxetine 4) fluconazole+duloxetine	With concomitant use of brexpiprazole with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; decrease the brexpiprazole dosage [see drug insert dosage and administration (2.5)]
Strong CYP3A4 Inducers *Examples*: rifampin, St.John's wort	With concomitant use of brexpiprazole with a strong CYP3A4 inducer, increase the brexpiprazole dosage [see drug insert dosage and administration (2.5)]

H. DATA SAFETY AND MONITORING PROCEDURES

Evaluation of Adverse Events

An adverse event ("AE") is "any untoward occurrence in a human subject participating in research". The event is undesirable and has an unintended outcome, but is not necessarily unexpected. The event may have been described in the informed consent as a risk of the study.

Adverse events include clinically significant abnormal laboratory or ECG findings, a symptom, or disease temporally associated with the use of a study drug, or the progression of disease, whether or not related to the study drug.

Illnesses present prior to the subject signing the ICF are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs.

Evaluation of Serious Adverse Event:

A serious adverse event ("SAE") includes:

- The death of a study subject, whether related to an study drug or not related
- A reaction which, in the opinion of the investigator, threatens the study subject with risk of death
- A disability or incapacity which, in the opinion of the investigator, causes substantial disruption of a study subject's ability to conduct normal life functions
- Hospitalization or extension of an existing hospitalization (excluding elective hospitalization for conditions unrelated to the study)
- A birth defect in an offspring of a study participant, regardless of the time after the study the congenital defect is diagnosed
- Any intervention required to prevent one of the above outcomes

Relatedness/Expectedness to the Study Drug

Related: Associated of having a timely relationship with the study agent or procedures; a reasonable possibility exists that an outcome may have been caused or influenced by the study in question (e.g., administration of a study drug), although an alternative cause/influence may also be present. Related events may be *definitely, probably, or possibly* related.

Unrelated: Unassociated or without a timely relationship to the study agent or procedures; evidence exists that an outcome is definitely related to a cause other than the event in question (e.g., underlying disease, environment).

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the investigator (or designated sub-investigator) according to his/her best clinical judgment.

Unexpected Adverse Event: - the adverse event is not an anticipated event for the study drug (not listed in the drug insert) and is not explained in the Informed Consent Statement that the study subject signed.

Monitoring and Reporting of Adverse Events

Continuous data and safety monitoring will be conducted by the PI. Any adverse effect reported to study personnel will be reviewed with the PI or sub-investigator who will determine whether they are mild, moderate or severe and the likelihood (definitely/possible/probable) that it is related to the study medication. All AEs will be followed until resolution, until deemed stable by the investigator or until the subject is deemed by the investigator to be lost to follow-up

Intensity	**Definition**

Mild	Causes transient or mild discomfort ; no limitation of usual activities; no medical intervention required.
Moderate	Causes mild to moderate limitation in activity; some limitation of usual activities: no or minimal medical intervention or therapy is required.
Severe	Causes marked limitation in activity; some assistance is usually required; medical intervention or therapy is required; hospitalization is probable.

The PI is ultimately responsible for assessing and reporting all adverse events as outlined in the protocol. The assessment of AEs may be delegated to a medically qualified Sub-Investigator, trained on this study protocol, who is listed on the FDA Form 1572 or equivalent document, and on the delegation of authority form. The PI or investigator will report adverse events to the IRB in accordance with IRB guidelines.

Reporting of Serious Adverse Events

All SAEs will be reported to UMass by the PI through telephone or email within 24 hours of discovery, using the form provided by the lead site, UMass. In the event of a SAE, the PI or designee will notify the lead site PI, Dr. Xiaoduo Fan by phone or email within 24 hours of the event and will email supporting documentation within 48 hours of the event and then as relevant data is available within the following week.

The PI must inform the IRB immediately regarding any AE (does not have to be causally related) that is both serious and unexpected; or that represents a series of AEs that, on analysis, is unanticipated, or occurs at an unanticipated frequency, or otherwise represents an unanticipated safety risk to the study subject. The IRB may subsequently choose to modify the informed consent or request changes to the protocol.

Occasionally, after a patient completes the study, a piece of data is missing or that we come to understand that it would be helpful to ask an additional question of all participants. For this reason, participants will be asked as part of the consent process if they are willing to be contacted after their study participation ends.

Protocol Deviations and Waiver

Protocol Waivers

Protocol waivers will be considered on a case by case basis by the principle investigator for this study.

Procedure for Non-Compliant Subjects

Problems related to symptoms of schizophrenia and substance dependence can cause a number of challenges to carrying out the protocol with a given participant, including: missed appointments, visits outside of the window, inability to complete all study assessments, not taking medication correctly, and not returning medication containers and extra pills. Such events will not be considered protocol deviations unless they impact a participant's safety or the scientific validity of the study.

Subjects who miss a study visit will be allowed (at the discretion of the PI) to make up that visit within that week. Subjects who withdraw consent will no longer have data collected for the study.

Protocol Deviation
Major and Minor Protocol Deviation

	Major Protocol Deviation	**Minor Protocol Deviation**
Definition	A deviation that **<u>may</u>:** Impact subject safety, Affect the integrity of study data, and/ or Affect the subject's willingness to participate in the study.	A deviation that **<u>does not</u>:** Impact subject safety, Compromise the integrity of study data, and/ or Affect the subject's willingness to participate in the study.
Examples *(not all-inclusive)*	Failure to obtain informed consent Informed consent obtained by an unauthorized individual Enrollment of a subject who did not meet eligibility criteria for whom a protocol exception was not obtained Performing a study procedure that is not approved by the IRB and/or is not in the protocol Failure to perform a required lab test that, in the opinion of the Site Investigator, may affect subject safety or data integrity Failure to perform or follow a study procedure that, in the opinion of the Site Investigator,	Implementation of unapproved recruitment procedures Only a photocopy of the signed/ dated consent form is available (the original is missing) Pages are missing from the signed/ dated informed consent form Use of invalid consent form (i.e. without IRB approval or outdated/expired form) Study procedure conducted out of sequence Failure to perform a required lab test Missing lab results

	may affect subject safety or data integrity Failure to follow safety (AE) management plan Failure to report a SAE to the IRB and/or Coordination Center	Over-enrollment Enrollment of subjects after IRB approval of the study has expired Failure to submit a continuing review application to the IRB before study expiration
Reporting Requirements	Record the date discovered, date occurred, description of event in the Protocol Deviation Log. Notify the UMass within 24 hours. Report to local IRB	Record the date discovered, date occurred, description of event in the Protocol Deviation Log. Notify UMass. Report to local IRB as per institutional policy

I. DOCUMENTATION OF DATA

Case Report Forms

The case report forms (CRF) will be collected using an electronic data capture (EDC) system RedCap. The study team will document subject data with paper CRF individual subject binders which will serve as the source data. The data entry on RedCap will be completed by designated study staff. This should be completed soon after the subject completes the study visit.

Data will be stored on the REDCap servers within the regulated environment at UMass Medical School (UMMS). REDCap servers are maintained by Information Technology and includes physically secure and electronically protected portion of the data center with its own insulated network space labeled “the Regulated Environment” to provide a secure environment for the storage and handling of sensitive electronic data including protected health information (PHI) and protected personal information (PPI). The Regulated Environment is securely housed within the IT data center meaning physical access is limited to only those IT professionals employed by IT with a job related need and with proper electronic identification. The servers are backed up nightly, properly updated and patched, protected with anti-virus and anti-spyware software.

Electronic access to sensitive data resources within the regulated environment is controlled using the highest standard of proven network architecture. Data will be transferred into the regulated environment via direct data entry, controlled web interface form-fill-out into a REDCap database.

Data Capture, Review and Validation

Study specific data that has been outlined in the protocol will be entered into the clinical database via the EDC system by designated site staff in accordance with the eCRF

Completion Guidelines. Data is verified electronically using a series of on-line programmed edit checks that have been created by the clinical data manager and programmed by the clinical data programmer or designee. Data discrepancies will be brought to the attention of the site staff and investigated by the clinical monitor and site study coordinator. The clinical monitor(s) will review and verify all eCRF data against acceptable source documentation during scheduled monitoring visits. The clinical monitor will work closely with the site study coordinator to address any discrepancies which have been found so that resolutions can be made and documented into the clinical database.

Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site.

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

Record Retention

All documents pertaining to the study, including all versions of the approved study protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act (HIPAA) documents, eCRFs, source documents (i.e., subject records, hospital records, laboratory records, medication records, etc.), and other study-related documents will be retained at the study site for 5 years after the study ends.

The PI must notify and obtain approval in writing from the UMass prior to destruction of any study records or provide an opportunity for the UMass to collect such records. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with UMass, to a mutually agreed upon designee and specified timeframe.

Data Confidentiality

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of all study data and by security protocols for all data capture systems. All users of the EDC system will be tracked and provided access in a secure fashion following established SOPs for this process.

As with all research data, information gathered by the study will be used only for aggregate analysis; it will not be released with any information that identifies research participants. Pharmacogenetic information, in particular, will be coded and unlinked to

individual respondent identifiers. The lead study site will apply for a Certificate of Confidentiality in order to ensure the complete anonymity of subjects with regards to their drug use. If approved, the Certificate of Confidentiality will be extended to all other study sites. If and when a Certificate of Confidentiality is approved and extended for all sub-sites, language specifying this Certificate will be added to the Informed Consent Form.

Uses and risks related to data collection will be outlined in the informed consent and reviewed with the subjects.

J. MONITORING AND OVERSIGHT

Initiation of Study Sites

Prior to subject enrollment, site initiation visits will be conducted by UMass at all sub sites. The initiation visit is completed to ensure IRB approval is obtained and documented; all study staff are trained and clearly understand the protocol.

Site Monitoring

Through the study the lead site UMass will conduct investigational site monitoring to ensure overall quality and compliance with protocol and applicable regulations by all investigators. Such monitoring activities will be conducted on-site and remotely including telephone calls and emails. The site will receive notification prior to the on-site monitoring visit. The investigator and the study staff are expected to be available on the day of site visit to address any queries. During the on-site study visits, subject case report forms (CRFs) will be reviewed for completeness and protocol compliance.

Study Closeout Visit

Upon completion of the study, a study closeout visit will be completed to review all study files and regulatory documents. The monitor will ensure all regulatory documents are up-to-date and complete. All study documents should be retained for an appropriate time period as stated in the contract.

Other issues which will be reviewed at this visit include: possibility of site audits, publication policy, and ensuring that the Investigator will notify the local IRB regarding study closeout.

Medical Monitoring

The medical monitor for this trial will be a board certified psychiatrist designated by the lead site, UMass. The Medical Monitor will review all adverse events, review issues

related to subject eligibility, assess the benefits and risks of protocols on an ongoing basis, and work in collaboration with the IRB to identify safety signals and trends.

K. ETHICAL CONSIDERATIONS

Ethics Review

The study protocol, ICF and all relevant documents will be reviewed and approved by the local IRB prior to study initiation. A written IRB approval from the committee must be received by UMass before starting study enrollment. The protocol must be re-approved by the IRB upon receipt of protocol amendments and annually, as part of their IRB regulatory requirements and institutional procedures. The PI or designee is responsible for submitting all protocol changes, SAE reports, administrative letters etc. to the IRB according to their regulatory policies.

Ethical Conduct of the Study

The study will be conducted as per the protocol and will adhere to the GCP standards. The investigators and all study staff should be trained in GCP guidelines.

Informed Consent

The PI must ensure to clearly explain and provide oral and written information on the study purpose, procedures, risks and benefits of participating (including potential risks involving the study medications) to each subject and/or legal guardian. All information should be provided in language that is easy to understand. All subjects must be informed that their participation is voluntary and they can withdraw from the study at any time if they choose. If the subject chooses to participate, he/she or legal guardian must sign the informed consent form and when required, the caregiver must sign the caregiver ICF. Any questions, concerns, or ambiguities will be clarified by the site's PI or another study clinician prior to the patient signing consent.

L. STATISTICS AND DATA ANALYSIS

Intent-to-treat analysis and a mixed model approach will be conducted to estimate the pragmatic effects of brexpiprazole treatment on the number of days of substance use in the past week, substance craving, psychiatric symptoms and quality of life. The entire 12 week duration of treatment, including the 6-week switchover phase, will be included in the analysis. Polynomial time trends (e.g., slopes) will be used to fit the population mean response curve for the control group. Group-by-time interactions will be modeled as a function of time to fit between-group effects. Subject-specific parameters will be estimated to model individual subject deviations from the group mean. Baseline measures of substance use and clinical symptoms will also be included in the model as covariates.

REFERENCES

1. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990; 264(19): 2511-8.
2. DeQuardo JR, Carpenter CF, Tandon R. Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res. 1994; 28(3): 267-75.
3. van Dijk D, Koeter MW, Hijman R, Kahn RS, van den Brink W. Effect of cannabis use on the course of schizophrenia in male patients: a prospective cohort study. Schizophr Res. 2012; 137(1-3): 50-7.
4. Albanese MJ, Khantzian EJ, Murphy SL, Green AI. Decreased substance use in chronically psychotic patients treated with clozapine. Am J Psychiatry. 1994; 151(5): 780-1.
5. Buckley P, Thompson P, Way L, Meltzer HY. Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. Am J Psychiatry. 1994; 151(3): 385-9.
6. Sorensen G, Sager TN, Petersen JH, Brennum LT, Thogersen P, Hee Bengtsen C, et al. Aripiprazole blocks acute self-administration of cocaine and is not self-administered in mice. Psychopharmacology (Berl). 2008; 199(1): 37-46.
7. Wee S, Wang Z, Woolverton WL, Pulvirenti L, Koob GF. Effect of aripiprazole, a partial dopamine D2 receptor agonist, on increased rate of methamphetamine self-administration in rats with prolonged session duration. Neuropsychopharmacology. 2007; 32(10): 2238-47.
8. Brown ES, Jeffress J, Liggin JD, Garza M, Beard L. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. J Clin Psychiatry. 2005; 66(6): 756-60.
9. Moreira FA, Dalley JW. Dopamine receptor partial agonists and addiction. Eur J Pharmacol. 2015; 752: 112-5.
10. Maeda K, Sugino H, Akazawa H, Amada N, Shimada J, Futamura T, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014; 350(3): 589-604.
11. Fleischhacker WW. Aripiprazole. Expert Opin Pharmacother. 2005; 6(12): 2091-101.

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP as described in ICH guideline E6 and to hospital Institutional Review Boards/Ethics Committees.

_____

Clinical Site

_____ _____

Principal Investigator Signature Date

_____

Principal Investigator

Printed Name