STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

Official title: Aripiprazole for Bipolar Disorder and Alcohol Use Disorder

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The University of Texas Southwestern Medical Center at Dallas
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Protocol

Title: Aripiprazole for Bipolar Disorder and Alcohol Use Disorder

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IND: This study is exempt from IND requirements (FDA-Approved, Unapproved Use)

1. Introduction and Purpose:

Aripiprazole appears to be a promising potential treatment for alcohol use disorder (AUD), is currently FDA-approved for the treatment of bipolar disorder (BPD), and may be well suited for dual-diagnosis populations. However, its utility may be limited by poor tolerability that may be due to improper dosing, as well as the outcomes used and populations chosen for previous study. To address these problems we propose to 1) use a dual-diagnosis population because aripiprazole is well tolerated and useful for mood symptoms in patients with BPD, 2) use a dose of only 15 mg/day unless the patient qualifies for the exploratory phase or the patient is on strong CYP3A4 inducers which increase aripiprazole clearance and lower blood levels of aripiprazole, 3) use participants with high impulsiveness since this may predict a favorable aripiprazole response, and 4) use a primary outcome measure that is sensitive to aripiprazole effects. This study will be one of a very small number of controlled trials in BPD and substance use disorders, and will be an adequately powered trial in an important and under-researched population. Aripiprazole is potentially a low cost treatment since a generic formulation should be available prior to the end of the study. This study will include both English- and Spanish-speaking participants.

Primary Aim: Determine if aripiprazole as an add-on therapy is associated with a greater reduction in alcohol use than placebo therapy in outpatients with BPD or Schizoaffective Disorder (Bipolar Type) and alcohol use disorder.

Secondary Aim: 1) Determine if aripiprazole as an add-on therapy is associated with a greater reduction in alcohol craving than placebo therapy in outpatients with BPD or Schizoaffective Disorder (Bipolar Type) and AUD.

Additional Exploratory Analyses: 1) Determine if aripiprazole as an add-on therapy is associated with a greater reduction in manic and depressive symptoms than placebo therapy in outpatients with BPD or Schizoaffective Disorder (Bipolar Type) and AUD. 2) Determine whether changes in alcohol craving and mood occur before or after changes in alcohol use with aripiprazole. 3) Determine if impulsivity decreases with aripiprazole as compared to placebo and examine relationships between change in impulsivity and change in alcohol consumption. 4) Assess rates of attrition, safety and tolerability of aripiprazole. 5) Examine genotype as a predictor of response to aripiprazole. 6) Explore safety, tolerability and efficacy of an increase in aripiprazole from 15 mg to 30 mg at week 12 for those with at least one heavy drinking day at week 12. 7) Determine if inflammation decreases with aripiprazole as compared to placebo and whether change in an inflammatory biomarker is associated with change in clinical outcomes.

2. Background:

Drug and alcohol abuse are common in persons with BPD.[1-4] In a community-based study, persons with bipolar I disorder had a 46% lifetime prevalence of alcohol-related disorders compared to 14% in the population as a whole.[5] Odds ratio of alcohol dependence is 5.5 for bipolar I disorder and 3.1 for bipolar II disorder. BPD is also much more common in people with alcohol dependence than the general population, with a 6% prevalence in men (odds ratio 12) and 7% in women (odds ratio 5).[6] Although disulfiram is effective for highly motivated patients, lack of adherence and safety concerns limit its use.[7-9] Acamprosate is an effective

medication based on some,[10-12] but not all,[13] large randomized, controlled trials. Selective serotonin reuptake inhibitors (SSRIs) may decrease alcohol consumption in some persons.[14] Efficacy of SSRIs for alcohol use in AUD patients may vary depending upon alcoholic subtype, gender, presence or absence of major depressive disorder, and specific SSRI used.[14-19] Aripiprazole is a promising medication for AUD that has novel receptor binding properties. It is a dopamine D2 partial antagonist, a 5-HT1A partial agonist, a 5-HT2A antagonist, 5-HT2C partial agonist, and 5-HT7 antagonist.[20, 21] As a D2 partial antagonist, aripiprazole blocks dopamine at high dopamine concentrations, while augmenting dopamine at low dopamine concentrations. Thus, aripiprazole has the potential to "normalize" dopaminergic tone and may act in a region-specific fashion to either increase or decrease dopamine levels.[22] Consistent with this view are data suggesting that aripiprazole may stimulate D2 autoreceptors in the ventral tegmental area (a brain region thought to be involved in AUD)[23] and thereby reduce dopamine neurotransmission to the nucleus accumbens.[24] By modulating dopamine in specific brain regions, aripiprazole could be useful both during early abstinence (decreased dopamine) or relapse to drinking (high dopamine).[25] The affinity of aripiprazole for serotonin receptors may also have an impact on dopaminergic systems. Aripiprazole appears to modulate 5-HT, ultimately decreasing overall 5-HT output in the medial prefrontal cortex.[26] Through partial agonism at the 5-HT1A receptor and antagonism at the 5-HT2A receptor, aripiprazole decreases serotonin output in the medial prefrontal cortex. The increase in dopamine in the medial prefrontal cortex observed with aripiprazole is attenuated by 5-HT1A antagonists, suggesting that aripiprazole may increase dopaminergic transmission in this brain region, in part, by way of 5-HT1A partial agonism.[22] Aripiprazole might also decrease alcohol consumption directly through serotonergic systems. Consistent with this idea are studies suggesting that the 5-HT1A partial agonist buspirone may decrease alcohol consumption, although the effects may be mediated by its anxiolytic effects.[27] Aripiprazole decreases alcohol consumption in an animal model of high drinking behavior.[28]

To date, few randomized, controlled trials have specifically examined the pharmacotherapy of patients with BPD and AUD. Thus, more research is much needed in this important population. We examined a group of patients with BPD and substance use disorders (n=20) switched from their current atypical antipsychotic (generally quetiapine) to aripiprazole. Mean depression and manic symptom scores significantly improved. In the subset (n=17) with AUD, the switch to aripiprazole was associated with a reduction in both alcohol use and craving. Aripiprazole was well tolerated. Scores on scales for antipsychotic side effects (akathisia, extrapyramidal symptoms, abnormal movements) did not change significantly. The findings, while preliminary in nature, suggest that aripiprazole may be more effective in reducing alcohol use in patients with BPD and AUD than other atypical antipsychotics. Aripiprazole appears to be a promising potential treatment for AUD. However, its utility may be limited by poor tolerability that may be due to improper dosing, as well as the outcomes and population chosen. To address these problems we propose to 1) use a dual-diagnosis population because aripiprazole is well tolerated and useful for mood symptoms in patients with BPD 2) use a dose of only 15 mg/day except in an exploratory phase, unless the patient qualifies for the exploratory phase or the patient is on strong CYP3A4 inducers which increase aripiprazole clearance and lower blood levels of aripiprazole 3) use participants with high impulsiveness since this may predict a favorable aripiprazole response, and 4) use a primary outcome measure that is sensitive to aripiprazole effects.

3. Concise Summary of Project:

We will conduct a 12-week, randomized, double-blind, parallel-group, placebo-controlled study of aripiprazole in 132 persons with AUD and bipolar I, II, or NOS disorder. Primary Aim will be to assess change in alcohol use by the Timeline Followback (TLFB) method.[29, 30] Secondary Aim will include change in alcohol craving using the Penn Alcohol Craving Scale (PACS).[31] Changes in psychiatric symptoms (mania/hypomania and depression) and predictors of response will be assessed. Participants with ≥ 1 drinking day at week 12 will be enrolled in a 4-week extension phase with an upward titration to 30 mg/day for those in the active treatment group. The placebo group will remain on placebo.

At the participant's last visit, the participant will be detitrated according to the following schedule:

- If at **10 mg qAM:** 5 mg qAM for 2 days, then 2 mg qAM for 2 days
- If at **15 mg qAM:** 10 mg qAM for 2 days, then 5 mg qAM for 2 days, then 2 mg qAM for 2 days
- If at **30 mg qAM:** 15 mg qAM for 2 days, then 10 mg qAM for 2 days, then 5 mg qAM for 2 days, then 2 mg qAM for 2 days

If the patient is taking strong CYP3A4 inducers, the participant's last visit, the participant will be detitrated according to the following schedule:

- If at **10 mg qAM:** 4 mg qAM for 2 days
- If at **20 mg qAM:** 10 mg qAM for 2 days, then 4 mg qAM for 2 days
- If at **30 mg qAM:** 20 mg qAM for 2 days, then 10 mg qAM for 2 days, then 4 mg qAM for 2 days,

Subjects will be discontinued from the study if any of the following conditions occurs: change in diagnosis to other than bipolar I, II, or NOS disorder and AUD, development of active suicidal or homicidal ideation with plan and intent, worsening in mood symptoms, that in the opinion of the investigators requires discontinuation, pregnancy, development of severe or life-threatening medical condition, involuntary psychiatric hospitalization or incarceration, or significant alcohol withdrawal (e.g. delirium tremens) based on clinical judgment (increases in CIWA-Ar scores will initiate a careful clinical assessment of possible worsening of withdrawal symptoms).

4. Study Procedures:

Baseline: This visit will be split into two portions, Baseline 1 and Baseline 2.

For Baseline 1 (~3 hours), the psychiatric diagnoses will be confirmed by the structured clinical interview for DSM (SCID)[32], mania assessed via the Young Mania Rating Scale[33] (YMRS), depression via the Hamilton Rating Scale for Depression[34] 17-item version ($HRSD_{17}$), potential withdrawal symptoms from alcohol via the Clinical Institute Withdrawal Assessment of Alcohol Use-Revised[35] (CIWA-Ar), recent alcohol use (and, if present, other substance use) will be assessed using the Timeline Follow Back[29, 30] (TLFB) method, impulsivity will be assessed with the Barratt Impulsiveness Scale[36] (BIS-11), and blood will be drawn for complete blood count (CBC), Comprehensive Metabolic Panel (CMP, includes a liver panel with AST, ALT, as well as lipids), high-sensitivity c-reactive protein (hs-CRP), gamma glutamyl transferase (GGT), and carbohydrate-deficient transferring (CDT). If the subject elects to participate, blood will also be collected for genotyping.

A urine sample for drug screen and pregnancy test (if applicable), psychiatrist assessment, physical exam, collection of weight and vitals can be completed at either Baseline 1 or Baseline 2.

For Baseline 2 (~1.5 hours), recent depressive symptoms will be assessed via the Inventory of Depressive Symptomatology–Self-Report[37-40] 30-item version ($IDS\text{-}SR_{30}$), and drinking behavior will be characterized using the Penn Alcohol Craving Scale[31] (PACS), safety and side effects will be assessed with the Psychobiology of Recovery in Depression III - Somatic Symptom Scale[42] (PRD-III), the Abnormal Involuntary Movement Scale[43] (AIMS), Barnes Akathisia Scale[44] (BAS) and Simpson-Angus Scale[45] (SAS), and Go/No-go task.[46, 47]. The Treatment Impressions Inventory (TII) is a survey about the participants' feelings and impressions towards medical treatment. The TLFB will be repeated to account for drinking behavior since the last visit and CIWA-Ar will account for any withdrawal symptoms. The aripiprazole or placebo capsules will be initiated at 2 mg/day in the morning, increased (if well tolerated) to 5 mg at week 1, 10 mg at week 2 and 15 mg/day (or equivalent placebo) at week 3. Participants taking concomitant medications that are strong inhibitors of the 3A4 or 2D6 isoenzymes will be titrated to a maximum dose of 10 mg/day. Strong CYP3A4 inhibitors are the following: Atazanavir, Boceprevir, Clarithromycin, Cobicistat, Conivaptan, Curcumin, Danazol, Danoprevir, Darunavir, Delavirdine, Diltiazem, Ditiocarb, Econazole, Efavirenz, Elvitegravir, Ergotamine, Idelalisib, Indinavir, Itraconazole, Ketoconazole, Lonafarnib, Loperamide, Lopinavir, Methimazole, Midostaurin, Naloxone, Nefazodone, Nelfinavir, Nilotinib, Posaconazole, Ribociclib, Ritonavir, Saquinavir, Stiripentol, Telaprevir, Telithromycin, Terfenadine, Tipranavir, Troleandomycin, Voriconazole. Strong CYP2D6 inhibitors are the following: Thioridazine, Paroxetine, Cinacalcet, Bupropion, Methotrimeprazine, Fluoxetine, Midostaurin, Propafenone, Glycerol phenylbutyrate, Halofantrine, Cisapride, Dacomitinib, Orphenadrine, Quinidine. For patients taking strong CYP3A4 inducers, the aripiprazole or placebo capsules will be initiated at 4 mg/day in the morning, increased (if well tolerated) to 10 mg at week 1, 20 mg at week 2 and 30 mg/day (or equivalent placebo) at week 3. Participants taking strong CYP3A4 inducers will not be enrolled in the extension phase.

Strong CYP3A4 inducers are the following: Nevirapine, Rifabutin, Rifampicin, Carbamazepine, Fosphenytoin, Pentobarbital, Phenobarbital, Phenytoin, Primidone, Rifapentine, Enzalutamide, Lumacaftor, St. John's Wort, Mitotane, Apalutamide, and Quinine.

Week 1, 2, 3, 5, 7, 9, 10, 11 (~2 hours each): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, and a urine sample will be collected for a drug screen. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected. In addition, all participants will receive one-hour sessions of manual-driven Medical Management (MM), specifically designed for persons with BPD and substance abuse, provided by an experienced therapist.

Week 4, 8 (~2.5 hours each): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, MM, and a urine sample will be collected for a drug screen and pregnancy test. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected. Blood will be drawn for CBC, CMP, GGT, and CDT.

Week 6 (~2.5 hours): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, GNG, MM, and a urine sample will be collected for a drug screen. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected.

Week 12 (~3.5 hours): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, GNG, BIS-11, MM, and a urine sample will be collected for a drug screen and pregnancy test. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected. Blood will be drawn for CBC, CMP, hs-CRP, GGT, CDT, lipids, and for aripiprazole levels. An exit survey will also be administered to participants evaluating their perception of in-person vs. virtual study visits. In the event of early discontinuation, the survey will be administered at the last available study visit.

At the end of the week 12 treatment phase, participants in both treatment arms who are taking 15 mg/day of aripiprazole (or placebo) and with at least one heavy drinking day will be asked to continue in a 4-week extension phase. Participants taking 3A4 or 2D6 inhibitors will be excluded from this phase. Those in the active treatment group will be increased to 30 mg/day while those in the placebo arm will remain on placebo.

Week 14 (~1 hour): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, MM, and a urine sample will be collected for a drug screen. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected.

Week 16 (~3 hours): Subjects will complete the YMRS, $HRSD_{17}$, CIWA-Ar, TLFB, IDS-SR_{30}, PACS, PRD-III, AIMS, BAS, SAS, MM, and a urine sample will be collected for a drug screen and pregnancy test. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected. Blood will be drawn for CBC, CMP, GGT, and CDT.

Participants will be paid for their time and inconvenience per visit, starting with $60 at Baseline 1 and then $50 at Baseline 2, $70 for week 12, $40 at weeks 1, 2, 3, 5, 6, 7, 9, 10, 11 and $50 at weeks 4 and 8. Participants will also receive a $2 bonus beginning at Baseline 2 that increases by $2 each time an appointment is attended and resets back to $0 if an appointment is missed. These payments will be completed via the ClinCard system. DART bus or rail passes will be provided. After study completion, standard psychiatric care will be provided until referral is arranged.

Participants will be paid $50 at week 14 and $60 at week 16. A phone assessment will be conducted at week 18 for all participants to evaluate mood, drinking, potential side effects, and confirm follow-up care plan.

At Baseline 1, participants who are found to be ineligible based on the inclusion/exclusion criteria will be paid $20 and provided with 2 DART passes.

5. Sub-Study Procedures:

Participants will be offered an optional genetic component of their study participation and will not be prevented from participating if they choose to not contribute to this genetic component. Additional blood (20mLs) will be drawn if this component is elected. These blood samples will be sent for genotyping to UT Southwestern McDermott Center for Human Growth and Development. Genetics studies implicate the T102C HTR2A polymorphism,[48, 49] and -1438 A/G polymorphism of the serotonin 2A (5-HT2A) receptor gene,[50] as well as the rs7916403 in serotonin receptor gene HTR7 on chromosome 10q235,[51] (both receptors with affinity for aripiprazole) in alcohol dependence. Impulsivity in alcohol dependence is also associated with the -1438A polymorphism in the promoter region of the 5-HT2A receptor.[52] The L/L genotype of the 5-HTTLPR promoter region of the serotonin re-uptake transporter (5-HTT) is associated with early onset of AUD and reduction in alcohol use with ondansetron.[53-55] Alcohol-dependent persons homozygous or heterozygous for the seven (or longer)-repeat allele of the DRD4 VNTR responded to olanzapine with reductions in cue-elicited craving as well as alcohol consumption.[56] We will also consider adding additional genetic analyses if promising new associations should emerge (e.g. a predictor of aripiprazole response for mood symptoms), based on the available literature at the time of the analysis.

6. Criteria for Inclusion of Subjects:

- Outpatient men and women age 18-70 years old with bipolar I, II or NOS disorder, or Schizoaffective Disorder (Bipolar Type) on the SCID and confirmed by interview with a psychiatrist.
- Current diagnosis of AUD with at least moderate severity (DSM-5 terminology).
- Alcohol use (by TLFB) of an average of 15 drinks per 7 days in the past 28 days prior to intake for men and an average of 8 drinks per 7 day period in the past 28 days prior to intake for women.
- If diagnosis of: Bipolar I, Bipolar NOS with history of mania, or Schizoaffective Disorder (Bipolar Type): Current mood stabilizer therapy (lithium, valproic acid, lamotrigine, gabapentin) with stable dose for ≥ 21 days prior to randomization. Patient who meet criteria for these diagnoses, but are not on mood stabilizers at the time of screening will be prescribed Lithium Carbonate (600mg daily) or Valproid Acid (500mg daily) prior to randomization, and are required to be on a stable dose for ≥ 21 days before starting Aripiprazole/placebo.
- Fluent in English or Spanish.
- SBP > 100 and < 165 and DBP > 60 and < 105 with no evidence of orthostatic hypotension

7. Criteria for Exclusion of Subjects:

- Cyclothymic disorder
- Schizophrenia
- Schizoaffective disorder (Depressed type)
- Any psychiatric disorder only due to alcohol use (alcohol-induced mood disorder)
- Any psychiatric disorder only due to substance use (substance-induced mood disorder)
- Any psychiatric disorder only due to a general medical condition

- Baseline HRSD17 or YMRS scores ≥ 35 to exclude those with very severe mood symptoms at baseline.
- Evidence of clinically significant alcohol withdrawal symptoms defined as a CIWA-Ar score of ≥ 10.
- Use of other substances is allowed if alcohol is the self-identified substance of choice and severity of other substance use disorder is ≤ the severity of the Alcohol Use Disorder (DSM-5).
- Current (last 28 days) treatment with an antipsychotic.
- Prior treatment with aripiprazole within the past year, or intolerable side effects to aripiprazole in lifetime.
- Current (last 28 days) treatment with naltrexone, acamprosate, disulfiram or topiramate.
- History of neuroleptic malignant syndrome or tardive dyskinesia.
- Vulnerable populations (e.g. pregnant, nursing, cognitively impaired, incarcerated).
- High risk for suicide defined as > 1 attempt in past 12 months that required medical attention, any attempt in the past 3 months or current suicidal ideation with plan and intent such that outpatient care is precluded.
- Intensive outpatient treatment (defined as ≥ 3 visits each week) for substance abuse (AA, NA meetings, or less intensive counseling at baseline will be allowed).

- Severe or life-threatening medical condition (e.g. hepatic cirrhosis) or laboratory or physical examination findings consistent with serious medical illness (e.g. dangerously abnormal electrolytes).
- AST or ALT > 3 times upper limit of normal.
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8. Sources of Research Material:

Clinical information will be obtained via the Structured Clinical Interview for DSM (SCID)[32], the Clinical Institute Withdrawal Assessment of Alcohol Use-Revised[35] (CIWA-Ar), the Hamilton Rating Scale for Depression[34] 17-item version ($HRSD_{17}$), Inventory of Depressive Symptomatology–Self-Report[37-40] 30-item version ($IDS\text{-}SR_{30}$), Young Mania Rating Scale[33] (YMRS), Penn Alcohol Craving Scale[31] (PACS), the Psychobiology of Recovery in Depression III - Somatic Symptom Scale[42] (PRD-III), Abnormal Involuntary Movement Scale[43] (AIMS), Barnes Akathisia Scale[44] (BAS) and Simpson-Angus Scale[45] (SAS), the Barratt Impulsiveness Scale[36] (BIS-11), the Go/No-go task.[46, 47], the Timeline Follow Back[29, 30] (TLFB).

Biological information will be obtained via blood drawn (18mLs) for laboratory analyses including a complete blood count (CBC) and Comprehensive Metabolic Panel (CMP, includes a liver panel with AST, ALT, as well as lipids), high-sensitivity c-reactive protein (hs-CRP), gamma glutamyl transferase (GGT), carbohydrate-deficient transferring (CDT), and aripiprazole levels. In addition, blood will be obtained at baseline (with the participant's consent) for genotyping (an additional 20mLs). A redraw may be requested if the first sample cannot be processed. A physical examination will be performed, weight obtained, and a urine sample collected for a drug screen and pregnancy testing.

9. Recruitment Methods and Consenting Process:

Participants will be recruited from the community through advertisements, by previous contact with the Psychoneuroendocrinology Research Program (PNE), and by referrals. Recruitment can be challenging in dual-diagnosis studies. By limiting enrollment to the subgroup of people with AUD who also have BPD or Schizoaffective Disorder (bipolar type), the rate of enrollment is generally not as fast as in studies of patients with AUD alone. However, we have had great success in recruiting this patient population. Over the past 16+ years, we have conducted some of the largest trials in BPD and substance use, including trials of quetiapine in patients with BPD and alcohol dependence with 90 and 115 participants. Our success in recruiting participants for our previous and ongoing studies demonstrates that we have the resources and contacts necessary to recruit participants for this project, and that we already have established measures in place to accomplish our recruitment goals. Potential participants who are referred to us or who respond via the various recruitment strategies will be contacted by telephone. Participants who remain interested and eligible for participation based on the telephone prescreen may be asked to come into our clinic for a diagnostic screening visit. Once noted as eligible, the staff member will discuss the procedures they will undergo if they choose to participate in the study. After reading the informed consent, study staff will discuss these issues with the potential participant and will answer any questions he or she may have about the study and participation. If the individual chooses to sign the informed consent document, he or she may begin testing for the study.

10. Potential Risks:

Study Procedure/Intervention

Aripiprazole may cause some, all or none of the side-effects listed below.

	Frequent 30% of subjects	Occasional 15% of subjects	Rare Less than 1% of subjects
Serious	Increased blood sugar	Uncontrolled movements Orthostatic Hypotension	Decreased white blood cell count Seizures
Less Serious	None	Headache Insomnia	None

		Anxiety Nausea Weight gain	
Minor	None	Constipation Vomiting	None

Black Box Warning

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

• Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS have been reported with aripiprazole.

A syndrome of potentially irreversible, involuntary, facial or body movements, called tardive dyskinesia, may develop in patients treated with antipsychotic drugs. The presence of these symptoms will be regularly evaluated.

Hyperglycemia (high blood sugar) has been reported in some patients treated with atypical antipsychotics such as aripiprazole. Glucose levels will be checked at entry to and during the study.

Increases in lipids (e.g. cholesterol) have been observed in some patients treated with atypical antipsychotics such as aripiprazole. Lipid levels will be checked at entry to and during the study.

Psychological Stress

Some of the questions asked as part of this study may make the participant feel uncomfortable. They may refuse to answer any of the questions, take a break or stop participation in the study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage sperm, which could cause harm to a child that a participant may father while in this study. Subjects who participate in this study and are sexually active, must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

Females: Subjects participating in this study while pregnant or breast-feeding an infant may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females are excluded from participating in the study. If a participant can become pregnant, a urine pregnancy test will be done and it must be negative before participation in this study. Subjects who participate in this study and are sexually active,

they and any person that they have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or “tubes tied”),

(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Implanon),

(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or

(4) an intrauterine device (IUD).

If a subject does become pregnant during this study, they are informed that they must tell the researchers immediately.

Risks of Blood Drawing

Risks associated with drawing blood from the arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

Placebo

Receiving a placebo means that no active medication will be administered for a health problem. If the problem becomes worse, participation in the research will stop. If this happens, the study doctor can discuss alternative care with the participant.

Psychological Stress

Some of the questions asked as part of this study may make the participant feel uncomfortable. They may refuse to answer any of the questions, take a break or stop participation in this study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep information confidential; however, this cannot be guaranteed.

11. Subject Safety and Data Monitoring:

The likely risks from the study are primarily medication side effects and the risk of untreated alcohol use disorder or bipolar disorder. Aripiprazole is reasonably well tolerated and may have fewer metabolic side effects than most other atypical antipsychotics. Approximately half of the subjects will not receive active medication during the study; however, they will receive frequent monitoring and follow-up appointments with a psychiatrist and research coordinator, in addition to Medical Management (MM), and their concomitant bipolar disorder medications (e.g. lithium,valproic acid, lamotrigine, gabapentin). Thus, both groups will receive care for both alcohol use disorder and mood symptoms. At the end of study, patients will be given follow-up appointments at treatment facilities we have worked with in the past, and will be followed by our group for at least 4 weeks (week 18 phone visit) to assure a smooth transition of care. If at any point in the study, including the follow-up phase, any participants develop a severe worsening of psychiatric symptoms that makes them a danger to themselves or others, they will be referred to the Parkland Hospital Psychiatry Emergency Room on campus for acute evaluation and care. If aftercare arrangements cannot be finalized prior to study completion then study physicians will continue to provide care until these arrangements are fully in place. These are our standard procedures for research studies and have been in place for over 17 years. Another potential risk is worsening of mood symptoms. To minimize this risk, participants will be receiving a mood stabilizer at baseline and changes in concomitant medications will be allowed when necessary. Potential pharmacokinetic or pharmacodynamic drug-drug interactions will be managed using inclusion, exclusion, and discontinuation criteria and dose adjustments. Clinical assessments are collected by trained and experienced staff members who will be able to reassure participants if they are distressed during study visits. If participants become fatigued or stressed during the testing, rest periods will be provided. Standard, appropriate measures will be used to minimize risk of infection during venipuncture.

Insomnia is challenging to treat in a dual-diagnosis population. To manage insomnia while avoiding the use of medications with abuse potential, we have developed an algorithm for the study (see below).

Management begins with adjustment of the time of administration of study and concomitant medication (e.g. changing valproic acid from 750 mg BID to 500 qAM and 1000 mg qHS) and sleep hygiene instructions (Appendix A). This approach is common clinical practice in patients with bipolar disorder. If this does not improve sleep, then melatonin is added. If this approach is not successful, then trazodone is added. Although trazodone is an antidepressant in high doses, a review of the literature does not reveal evidence of either improvement in depressive symptoms or induction of manic symptoms at modest nighttime doses. The next step is the use of ramelteon (a prescription melatonin receptor agonist). If these approaches fail to control the insomnia, then the combination of ramelteon and trazodone will be allowed. It is also important to note that insomnia is frequently a transient side effect with aripiprazole. Data from large aripiprazole trials suggest that the incidence of insomnia decreased from approximately 12% at week 1 to 5% at week 3 in patients who continued in the trials.[57] Thus, it may resolve in many cases without the use of concomitant medications.

Insomnia Management Algorithm

1) Adjustment of timing of administration of study drug and concomitant medications, current medications AND sleep hygiene instructions.
2) Melatonin
    a. Begin melatonin at 3mg po qHS—to be taken one to two hours prior to bedtime.
    b. If no significant improvement in insomnia, increase melatonin to 6mg po qHS—to be taken one to two hours prior to bedtime.
    c. If no significant improvement, discontinue melatonin and proceed to step #3.
3) Trazodone
    a. Begin trazodone at 25mg po qHS—to be taken 30-60 minutes prior to bedtime.
    b. If no significant improvement in insomnia, increase trazodone as tolerated to 50mg po qHS.
    c. If no significant improvement in insomnia, increase trazodone as tolerated to 100mg po qHS.
    d. If no significant improvement in insomnia, discontinue trazodone and proceed to step #4.
4) Ramelteon
    a. Begin ramelteon at 8mg po qHS—to be taken 30-60 minutes prior to bedtime.
    b. If no significant improvement, proceed to step 5.
5) Combination therapy using ramelteon and trazodone.

Fatigue and disturbance in attention may both be related to the sedating properties of aripiprazole. It appears to be a medication that can cause restlessness and insomnia, as well as fatigue, sedation and somnolence. These daytime side effects of aripiprazole will be managed as described above with 1) timing of study drug dosing (qHS rather than morning), and 2) adjustments in timing of concomitant medications (e.g. greater proportion of total dose in early evening than in the morning).

Finally, although not as common as the above side effects, nausea and vomiting are sometimes reported with aripiprazole. Nausea was uncommon in our pilot study (section 3.3.a) and in the aripiprazole study in alcohol dependence[25] but, perhaps due to the higher starting dose, was observed with greater frequency than placebo in the bipolar depression trial.[42] We will minimize this side effect with a low-starting dose and the use of a slower dose titration when needed. If nausea is reported, the participants will be instructed to take the study drug with a meal (per package insert aripiprazole can be taken with or without food).

Please note that all side effect management will be conducted in a double-blind fashion. In all of the aripiprazole trials noted above, side effects were also reported in the placebo group. Thus, the development of side effects does not necessarily suggest that the participant is taking aripiprazole.

In order to minimize the risks related to the use of placebo, we will schedule frequent appointments with a psychiatrist investigator and research coordinator. If participants have a worsening of symptoms, such as active suicidal ideation, study participation will be discontinued, and we will provide them with referrals for appropriate care.

All investigators and research staff will be available 24 hours a day. The consent form will have both daytime and nighttime numbers for reaching study personnel. Business cards for the research coordinator and psychiatrists will also be provided. In the event an investigator or research coordinator is on vacation or out-of-town, coverage will be provided, and both the research coordinator and UT Southwestern answering service are informed of the name and pager number of the physician-on-call. In the event of a medical or psychiatric emergency, appropriate medical advice will be provided including recommendations for emergency room evaluation if necessary. The PI and other physicians involved with the study have staff privileges at the Parkland and William P. Clements University Hospital Emergency Rooms, which are likely to be the most

commonly used hospitals by the participants. The physicians and other staff have extensive experience working with patients with bipolar disorder and substance use disorders.

All women of childbearing potential (premenopausal and without a clearly documented hysterectomy, ovariectomy or bilateral tubal ligation) must have a urine pregnancy test with negative results prior to receiving study medication. These participants will also be asked to use effective forms of contraception during the study. Pregnancy or failure to use contraceptives will result in discontinuation from the study.

Potential safety concerns will result in discontinuation from the study protocol. However, standard care will be provided until referral to another physician for further care can be arranged. The following conditions would require consideration of discontinuation from the study:

- Change in diagnosis to other than bipolar I, II, or NOS disorder and AUD.
- Development of active suicidal or homicidal ideation with plan and intent.
- Worsening in mood symptoms, that in the opinion of the investigators requires discontinuation.
- Pregnancy.
- Development of severe or life-threatening medical condition.
- Involuntary psychiatric hospitalization or incarceration.
- Significant alcohol withdrawal (e.g. delirium tremens) based on clinical judgment. Increases in CIWA-Ar scores will initiate a careful clinical assessment of possible worsening of withdrawal symptoms.

These are general guidelines. In all cases, physician judgment will be used to determine whether or not a participant can safely remain in the study. Some level of suicidal ideation is common in the participants we research. However, we want to take steps to prevent risk of suicidal acts. Thus, the emergence of intense suicidal thoughts with a clear plan (e.g. overdose) and the intent to act on the plan would require discontinuation from the study. However, recurrent suicidal thoughts accompanied by a clear understanding that the participant does not plan to act on these thoughts would not require discontinuation.

A breathalyzer will be used to assess whether or not the participant is currently intoxicated (defined in Texas as a blood alcohol level ≥0.08%). On rare occasions, patients in our alcohol treatment studies have arrived at our clinic intoxicated. We handle this on a case-by-case basis by asking them to remain at our clinic for several hours until their blood alcohol level has decreased and, if necessary, later calling a friend to take them home. We do not allow participants to leave our clinic while intoxicated. If a patient insisted upon leaving the clinic while intoxicated, we would call campus police.

For participant safety and the internal validity of the study, concomitant medications for bipolar disorder will be managed in order to prevent discontinuation due to symptoms unrelated to the primary outcome of alcohol use, while providing consistency and structure to the medication management.

The proposed study is placebo-controlled and in a group of patients with a major mental illness and substance abuse. Given the potentially vulnerable nature of the participants, in addition to the monitoring and review by the UT Southwestern IRB, we have implemented an additional data and safety monitoring plan that includes the formation of a Data and Safety Monitoring Board (DSMB).

<u>Adverse Events</u>

1) Exclusion criteria include active suicidal ideation, pregnant or nursing women, or prisoners to minimize risk to vulnerable populations or adverse events.
2) All adverse events will be discussed with and evaluated by a physician investigator as soon as reported by the subject.
3) Adverse events will be appropriately reported to the IRB and DSMB. The UT Southwestern IRB Policy it to only accept Adverse Events that are “Unexpected (in terms of nature, severity, or frequency) *and* Definitely or Probably related *and* Serious or otherwise suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Serious adverse events meeting these criteria are to be individually reported within two business days to the IRB. We will report serious adverse events to the NIAAA within 24 hours and can also report these adverse events to the IRB within 48 hours rather than two business days. We will report the adverse events that the IRB does not review to the DSMB for the study. Unexpected, but not serious, adverse events will be reported within 5 working days of our being informed by the patient of the occurrence of the event. Nonserious, expected adverse events will be reported to the IRB and DSMB in periodic summary reports. As part of this reporting process, the PI evaluates the severity of the adverse event, its relationship to the study, and whether changes in the protocol are warranted. Adverse events will also be reported to NIAAA in annual progress reports.

4) We will also report all AEs occurring during the follow-up period to the NIAAA in an annual report and will report reportable AEs to the IRB. AEs will also be reviewed at DSMB meetings
5) In addition to the IRB review of adverse events outlined above, the PI will meet weekly with staff and physicians to discuss any problems that arise that could compromise patient safety. When necessary, the IRB will be consulted for further guidance.
6) The PI, co-investigators involved with clinical care and the research coordinators will be available 24 hours each day to patients and other investigators should an emergency arise.

Data and Safety Monitoring Board

In addition to the safeguards listed above, we will form a Data and Safety Monitoring Board that will periodically review the project. This board will consist of Subroto Ghose, M.D., Ph.D. (chair), Marisa Toups, M.D. and Mary Ellen Bret, M.D.

Dr. Ghose is Associate Professor of Psychiatry at UT Southwestern. He completed a psychiatry residency at Georgetown University Medical School and a fellowship in neuropathology at the National Institutes of Health. Dr. Toups is Assistant Professor of Psychiatry at UT Southwestern. She works with the Department's Depression Center and has a K award focusing on biomarkers for depression from NIMH. Dr. Bret completed a psychiatry residency at the University of Texas Medical School at Houston and a geriatric psychiatry fellowship at UT Southwestern. She is currently Associate Professor of Psychiatry at UT Southwestern and director of the Parkland Hospital Geriatric Psychiatry Clinic. None of the proposed members is a co-investigator or consultant on the proposed grant or other grants by the PI, and none currently serve on the UT Southwestern IRB. Thus, the board will provide an independent review and oversight mechanism for the study.

As for the logistics of the proposed board, we propose that the members be unblinded so they can make a meaningful assessment of the data from both placebo and active medication groups. We currently have ongoing DSMBs for other NIH-funded clinical trials and have proposed a similar design for the proposed board. The board will meet immediately prior to the initiation of enrollment in the study, after 25, 50, 75 and 100 participants have been enrolled, and at the end of the study. The study's biostatistician will present safety data to the board for review, including changes in psychiatric symptom severity and alcohol use/craving. The PI (Dr. Brown) will attend the meeting at the beginning and end, but will not be present if any unblinded data are reviewed in order to preserve integrity of the blind. In addition, materials provided to the IRB, including serious adverse events (SAEs) leading to death, hospitalization or ER visits will be forwarded to board members. The board will review preliminary data on adverse events and outcomes. If, based on this review, the board feels that protocol modifications are needed, it will have the authority to modify safety procedures and temporarily or permanently discontinue enrollment if needed. At each DSMB meeting a careful consideration of stopping the study will be conducted. If the number of total SAEs in the aripiprazole group is ≥ 3 times higher than with placebo study, the data will be flagged for special consideration by the DSMB. The DSMB will carefully review the SAEs. Additional information, such as scores on each organ system assessed by the PRD-III side effects scale may be requested to guide decision making. The board will then provide written documentation and justification of a decision to continue or stop enrollment. This approach is based on the stopping rules suggested by Hedenmalm et al.[58] Because stopping rules are often reserved for larger, multisite trials, we modified the recommendations for a smaller study. Instead of using a predetermine significance, such as $p < .001$ to prompt consideration of discontinuation we use the value of three times greater than with placebo. We selected this approach because statistical significance might be virtually impossible to achieve with relatively uncommon, dichotomized events from relatively small numbers of participants. Rather than attempting to categorize the SAEs, which would result in very small numbers in each category, we will use total SAEs to prompt review. At this point the DSMB can review specific types of SAEs and look for patterns. We will review the proposed procedures of the DSMB with the NIAAA program official and seek their guidance and approval prior to enrollment.

12. Procedures to Maintain Confidentiality:

Blood specimens will be provided to Quest Diagnostics for analysis, removing identifying information (e.g., name) that could be linked to the patient's identity prior to sending for analysis. The blood provided to Quest will have the participant's date of birth to correctly link the results to the participant. The results of this test will be de-identified and added to the rest of the de-identified data. Once de-identified, only the identified investigators can learn/discover the names of participant.

Data Management Plan

All data related to the participant's participation in this study will be given a study ID which cannot be traced back to the patient except by study staff. All personal information which can identify the patient's identity will be kept separately from study documents and assessments. All clinical assessments will be collected in paper form and scores transferred to a computer database maintained on a password protected computer, on a secure server behind a firewall. The paper forms will be kept in binders marked only with the patient's study ID and will be kept in a locked room for the required time period following the completion of this study.

A Certificate of Confidentiality will be obtained for this study.

13. Potential Benefits:

Bipolar disorder is a severe, persistent, and common psychiatric illness that is associated with a staggering 46% lifetime prevalence of alcohol-related disorders, being associated with numerous adverse consequences including increased hospitalization, poor outcome during hospitalization, violence towards self and others, and treatment nonadherence. The atypical antipsychotic aripiprazole is a particularly promising medication which may lead to the development of effective treatments for patients with bipolar and alcohol use disorder. This rare placebo-controlled trial in patients with bipolar disorder and alcohol use disorder may be an important step forward toward advancing the successful treatment of this patient population. Minimal data are available on the treatment of persons with BPD and substance abuse. However, these illnesses occur together at high rates. Thus, the primary benefit of the study will be for persons with BPD or schizoaffective disorder biplar typeand alcohol use disorder to determine whether aripiprazole therapy will reduce alcohol use and craving. *There may, however, be some benefit to the subjects who participate in the study as they will receive a careful screening for mood symptoms as well as MM.* Approximately half of the subjects will receive an active medication that, in some cases, will likely improve their mood symptoms.

The primary risks of this study are medication side effects and the risk of receiving inactive medication, though aripiprazole appears to be a generally safe and a reasonably well-tolerated medication. We feel it is essential for this study that a placebo group be included as the efficacy of even standard medications in dual-diagnosis patients is not well established. Thus, the benefits of the study are great and will include a better understanding of the treatment of bipolar disorder with comorbid alcohol use disorder. This will be the first controlled study of this medication in patients with bipolar disorder and alcohol use disorder, and will provide valuable data on its efficacy in this population and the relationship between mood symptoms and drug use. Thus, we feel that the risks, though clearly present, are greatly outweighed by the benefits of this study.

14. Biostatistics:

Randomization: A biostatistician will perform the randomization, and we will stratify based on baseline use of lithium vs. anticonvulsant (valproic acid, lamotrigine, gabapentin) as a mood stabilizer and baseline drinks per drinking day of ≥ 8 and < 8 (based on use patterns in our prior studies in this population). In the event that a patient takes both lithium and an anticonvulsant, he or she will be stratified to the lithium group. Patients not taking a mood stabilizer will be stratified with the anti-convulsant group.

Primary Aim: Determine if aripiprazole as an add-on therapy is associated with a greater reduction in alcohol use than placebo therapy in outpatients with BPD or Schizoaffective Disorder (bipolar type) and alcohol use disorder.

Participants completing baseline and at least one post-baseline assessment will be used in the analysis (ITT sample). In the spirit of an ITT analysis, data will be collected even on participants who miss assessments or discontinue medication but continue in the study. Data on participants who do not complete the study will be analyzed up to the point of study discontinuation. A random regression that includes all data will be conducted with treatment group as the between-subjects factor; time as the within-subjects factor; and a group by time interaction term with drinks per drinking day (primary outcome), number of heavy drinking days, and number of drinking days, CDT, GGT, AST, and ALT (secondary outcomes) as the dependent variables. The model will allow for random slopes and intercepts while all other factors will be fixed effects. A secondary data analysis will be conducted using multiple imputation (MI) so the results from boantith analyses can be compared. SAS Proc Mixed will be used. The need for additional covariates, transformations of variables, as well as goodness of fit of the final model, will be investigated. The following covariates will be considered: age, gender, type of diagnosis, baseline BIS-11 and GNG scores, baseline use of substances other than alcohol, presence of anxiety disorder,

baseline use of psychotropic medications, and change in use of psychotropic medications. *C*ovariates will be included if they significantly improve the fit of the final model. An a priori alpha of 0.05 will be used for all other analyses. The influence of exit aripiprazole blood levels on the primary, secondary and exploratory aims will also be examined.

Secondary Aim: 1) Determine if aripiprazole as an add-on therapy is associated with a greater reduction in alcohol craving than placebo therapy in outpatients with BPD or Schizoaffective Disorder (bipolar type) and AUD. PACS scores will be compared between groups with an ITT sample and using a random regression as described above.

Additional Exploratory Analyses:

1) Determine if aripiprazole as an add-on therapy is associated with a greater reduction in manic and depressive symptoms than placebo therapy in outpatients with BPD or Schizoaffective Disorder (bipolar type) and AUD. Between-group differences in YMRS, $HRSD_{17}$ and $IDS\text{-}SR_{30}$ scores will be compared using a random regression as above.

2) Determine whether changes in alcohol craving and mood occur before or after changes in alcohol use with aripiprazole. We will explore correlations between baseline to exit changes in mood (e.g. $HRSD_{17}$) and alcohol use/craving assessments using a Pearson's correlation coefficient in aripiprazole and placebo groups. In addition, a panel model with lagged effects[59] will be used to analyze 12-week longitudinal data (SAS Proc Panel) in order to explore serial correlations between changes in alcohol use with mood and craving with lagged effect (e.g. one week, two week). Panel model will be constructed for each alcohol use, alcohol craving, depressive and manic symptom, and cognitive outcome, and test if change in alcohol use follows changes in craving, mood or cognition at subsequent visits and vice versa.

3) Determine if impulsivity decreases with aripiprazole as compared to placebo and examine relationships between change in impulsivity and change in alcohol consumption. BIS-11 and GNG scores will be compared between groups as with the Primary Aim above. Correlations between BIS-11 scores and GNG scores, and alcohol use measures, as well as lagged effects will be compared as with Exploratory Aim 2 above.

4) Assess rates of attrition, safety and tolerability of aripiprazole. Length of time in the study in weeks will be compared between groups using Cox proportional hazards regression. Scores on the PRD-III, AIMS, BAS and SAS will be compared between-groups as with the Primary Aim above.

5) Examine genotype as a predictor of response to aripiprazole. The purpose of this analysis is to identify whether genotype (e.g. 1438A polymorphism in the promoter region of the 5-HT2A receptor, LL compared with the LS/SS of the 5-HTTLPR promoter region of the 5-HTT) is a moderator of treatment effect. Treatment effect is determined by treatment group, main effect and treatment group by time interaction effect estimated from the random regression model described for the primary aim. The potential moderator of genotype will be included in the random regression model for the primary outcome along with variable by treatment group interaction and variable by treatment group by time interaction. Significance for either interaction term would indicate that the variable is a moderator.

6) Explore safety, tolerability and efficacy of an increase in aripiprazole from 15 mg to 30 mg at week 16 for those with at least one drinking day at week 12. All lab values and other safety measures will be compared between treatment groups at week 16 using t-test or chi-square test, as appropriate. Scores on outcomes measures including alcohol use (e.g. heavy drinking days) and side effect scales (e.g. BAS) will be compared between groups at week 16 using analysis of covariance. Week 12 value of the outcome will be the covariate.

7) Determine if inflammation decreases with aripiprazole as compared to placebo and whether change in an inflammatory biomarker is associated with change in clinical outcomes. Analysis described for Exploratory Aim 3 (above) will be used with hs-CRP data to test this aim.

Power analysis: One potential guide to calculate effect size comes from a recent study comparing naltrexone alone and with aripiprazole for alcohol dependence.[60] The results of that study have not been published yet. However, the abstract shows that the sample size was 21 per group, and the p-value was .009 for a between-group comparison of heavy drinking days. If we assume a two-sample t-test, then from the above information we can compute the smallest value of the quantity (placebo mean – aripiprazole mean) / standard deviation that will produce a p-value of .009. This quantity (i.e. the effect size) is 0.841. This effect size would be classified as a large effect size which may not be reproducible in another sample with a different design and patient population. If we assume a medium effect size of 0.5, 80% power, a two-sided t-test, and

alpha=.05 then a total sample size of 128 would be required. All subjects with post-baseline data, not just completers, will be included in the analysis. However, we frequently see some attrition (approximately 3%) between baseline and the first post-baseline assessment, therefore, final sample size will be 132.

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