A Supportive Care-Drug Intervention Study

A Randomized, Double-Blind 4-Week Study

to Evaluate the Impact of AXS-05 on Smoking Behavior

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DUKE CANCER INSTITUTE

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2. LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse event
AXSOME	Axsome Therapeutics Incorporated
AXS-05	Novel fixed dose combination of Dextromethorphan-Bupropion (Axsome Therapeutics Inc.)
AUDIT-C	Alcohol Use Disorders Identification Test
BID	Twice a day
BPRS	Brief Psychiatric Rating Scale
BUP	Bupropion
CBC	Complete Blood Count
CES-D	Centers for Epidemiologic Studies - Depression Scale
CO	Carbon monoxide
CPD	Cigarettes per day
CRC	Clinical Research Coordinator
CRS	Clinical Research Specialist (Duke name for Research Assistant)
CSC	Center for Smoking Cessation
C-SSRS	Columbia-Suicide Severity Rating Scale
DAST	Drug Abuse Screening Test
DSMB	Data and Safety Monitoring Board
DUHS	Duke University Health System
DXM	Dextromethorphan
FDA	Food and Drug Administration
FTND	Fagerström Test of Nicotine Dependence
GAD-7	Generalized Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IR	Immediate-release
IRB	Institutional Review Board
mCEQ	Modified Cigarette Evaluation Questionnaire
MDQ	Mood Disorder Questionnaire
MMS	Modified Mini Screen
MNWS	Minnesota Nicotine Withdrawal Symptoms Scale
MPSS-2	Mood and Physical Symptoms Scale
NCI	National Cancer Institute
NIH	National Institutes of Health
SAE	Serious Adverse Event
WBC	White Blood Cells
MPSS	Mood and Physical Symptoms Scale
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire-9
PSQI	Pittsburg Sleep Quality Index
PSS-4	Perceived Stress Scale-4
ROS	Review of Systems
SAE	Serious adverse event
SR	Sustained-release
STAI	State-Trait Anxiety Questionnaire

TRD Treatment Resistant Depression

3. PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1. PURPOSE

Product Name: AXS-05

Development Phase: Phase 2

Protocol Title: A Randomized, Double-Blind 4-week Study to Evaluate the Impact of AXS-05 on Smoking Behavior

This research study is designed with the purpose of evaluating a new drug, combination Dextromethorphan-Bupropion (AXS-05), for its effect on smoking behavior.

Primary Objective

1. To evaluate the impact of AXS-05 compared to Bupropion (BUP) on change in smoking intensity from baseline to the 3-Week Follow-Up Visit. Smoking intensity refers to the total amount of smoke inhaled by the smoker and includes the number of cigarettes smoked per day. Smoking intensity will be assessed as a latent variable modeled through three predictive factors: 1. Salivary cotinine, which will be assessed at all study visits, 2. Expired carbon monoxide (CO) breath testing at all study visits and 3. Number of cigarettes smoked per day assessed via daily smoking diaries.

Secondary Objectives (Smoking Behavior)

2. To compare AXS-05 to BUP on smoking abstinence within a 7-day Abstinence Test conducted between the 3-Week Follow-up and 4-Week Follow-up Study Visits. Smoking Abstinence will be assessed by self-report diaries and biochemically confirmed via expired CO and salivary cotinine.

Secondary Objectives (Covariates and Potential Moderators)

3. To assess specific baseline variables for an association with smoking behavior outcome, listed above. Baseline variables assessed will include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, and self-efficacy. If a baseline variable is found to be associated with change in smoking behavior, it will be treated as a covariate in a secondary analysis of smoking behavior and assessed as a potential moderator of treatment effect.

Secondary Objectives (Adherence, Side Effects, and Tolerance)

4. To compare AXS-05 to BUP on adherence to self-administered drug through Medication Use diaries
5. To compare AXS-05 to BUP on tolerability through weekly, open-ended survey to assess potential side effects.
6. To compare AXS-05 to BUP on the incidence of adverse events or serious adverse events utilizing FDA accepted reporting guidelines on these outcomes.

Secondary Objectives (Urinary Levels of DXM)

7. To measure urine drug levels of Dextromethorphan (DXM) at weeks 1-4 and assess potential correlation of these levels with smoking behavior and side effects.

Secondary Objectives (Potential Mediators)

8. To compare AXS-05 to BUP on changes from baseline vs. weeks 1-4 Follow-up Visits on the following: smoking urges, withdrawal symptoms, smoking reward, stress, anxiety, depression, sleep disturbance, and agitation.
9. To compare AXS-05 to BUP on change from baseline to weeks 1-4 Follow-up Visits on daily assessment of the following: urge frequency, urge severity, and irritability.

Hypotheses

This protocol is hypothesis-supporting and hypothesis-testing.

Primary Hypothesis

1. Participants allocated to AXS-05 vs. BUP will demonstrate significant reduction in total smoking intensity from baseline to the 3-Week Follow up visit. Smoking intensity will be assessed as a latent variable modeled through 3 predictive factors: 1. Salivary cotinine, which will be assessed at all study visits. 2. Expired carbon monoxide (CO) breath testing at all study visits and 3. Number of cigarettes smoked per day will be verified objectively and salivary cotinine level.

Secondary Hypotheses (Smoking Behavior)

2. Participants allocated to AXS-05 vs. BUP alone will demonstrate a significantly higher smoking abstinence rate within the 7-day Abstinence Test conducted between the 3 week Follow-up and 4 week Follow-up Study Visits. Smoking Abstinence will be assessed via self-reported smoking abstinence (not one puff of one cigarette) with biochemical confirmation via expired CO breath test and salivary cotinine.

Secondary Hypotheses (Covariates and Potential Moderators)

3. Potential baseline predictors of tobacco use will not be associated with smoking behavior outcomes listed in objectives 1-6; these predictors include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, and self-efficacy.

Secondary Hypotheses (Adherence, Side Effects, and Tolerance)

4. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference on adherence to self-administered drug via Medication Use Diaries.
5. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference in the incidence of side effects through weekly open-ended surveys on potential side effects.
6. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference on adverse events or serious adverse events utilizing FDA accepted reporting guidelines on these outcomes.

Secondary Hypotheses (Urinary Level of DXM)

7. Participants allocated to AXS-05 vs. BUP alone will demonstrate the following with regard to urinary drug levels at each medication assessment visit: 1. Relatively stable urinary drug levels of DXM (< 50% below or above the mean), 2. A majority of participants will show urinary DXM concentrations that are in the "expected therapeutic range" for tobacco dependence treatment (30 ng/ml), 3. There will be a correlation between DXM levels and smoking behavior outcomes (objective 2), 4. Urinary levels of DXM that are above the mean will not be associated with a higher incidence of side effects or adverse events (objectives 4-6) when added to BUP and compared to BUP alone.

Secondary Hypotheses (Potential Mediators)

8. Participants allocated to AXS-05 vs. BUP will demonstrate the following: 1. A significant reduction in smoking urges, withdrawal symptoms, stress, anxiety, depression, sleep disturbance, agitation from baseline to all four post-drug initiation time points, 2. The change in in smoking urges and withdrawal symptoms will be significantly associated with change in smoking behavior assessed through objective 2.
9. Participants allocated to AXS-05 vs. BUP will demonstrate a significant reduction in urges and improvement in irritability from baseline to weeks 1-4 based on urges and irritability Diary entries.

3.2. BACKGROUND AND SIGNIFICANCE

1. The Study Therapy: The overarching goal of this proposal is to conduct preliminary testing of AXS-05 (a fixed dose combination of 105 mg of sustained-release (SR) Bupropion (BUP) and 45 mg of immediate-release (IR) Dextromethorphan (DM)) for its effect on smoking behavior. Dextromethorphan (DXM), a widely used over-the-counter cough suppressant, crosses the blood-brain barrier easily. DXM has been shown to block α3β4 nicotinic acetylcholine receptors and N-methyl-D-aspartate (NMDA) receptors, is a serotonin and norepinephrine reuptake inhibitor, and is a sigma-1 receptor agonist. Studies at our center have shown that administration of DXM leads to decreased self-administration of nicotine in nicotine-dependent rats in a dose-dependent manner (see #6 below in this section). DXM has not, however, been studied for its effect on tobacco use in humans.

DXM, when taken alone (e.g. when it is used as a cough suppressant), would not be expected to be useful for treatment of nicotine dependence in humans. Therapeutic concentrations of DXM are required to bind the receptors that impact neurotransmitters that are important in the treatment of nicotine dependence; however, it is not possible to attain these concentrations of DXM in humans when it is dosed as a single agent because of its rapid metabolism via CYP2D6. Because approximately 95% of DXM that is ingested is quickly metabolized into dextrorphan via the CYP2D6 pathway, plasma concentrations of DXM are negligible when it is administered alone. The metabolite dextrorphan is quickly glucurodinated and therefore does not easily cross the blood-brain barrier and thus would not be expected to have a meaningful impact on nicotine self-administration in humans. An innovative approach to attain therapeutic concentrations of DXM is to co-administer it with an inhibitor of its metabolism. Such an approach would allow for attainment of plasma concentrations that have been shown to result in the binding of neural receptors that impact nicotine self-administration (See #6 below in this section).

Bupropion (BUP) is a well-characterized, FDA approved medication for smoking cessation that has also been shown to inhibit the metabolism of DXM. When various doses of BUP – including doses that are commonly prescribed for smoking cessation (e.g. 150 mg or less) – are co-administered with DXM to healthy volunteers, a significant increase in DXM plasma levels is observed (See Investigators Brochure Version 4.0 [IND 129633] Section 5.1.1: AXS-05 (Bupropion and Dextromethorphan Pharmacokinetics). This finding, together with the finding that similar DXM levels reduce nicotine self-administration in nicotine-dependent rats, suggests that it may be possible to develop a drug product that combines safe, commonly used doses of DXM and BUP that would be well-tolerated and result in a reduction in smoking behavior in humans.

Currently, the pharmaceutical development company Axsome Therapeutics Inc. (Axsome) is developing and testing an oral fixed-dose combination 45 mg IR DXM with 105 mg SR BUP to achieve therapeutic concentrations of DXM. The BUP in this combination serves to increase the bioavailability of DXM, and act as a norepinephrine and dopamine reuptake inhibitor and a nicotinic acetylcholine receptor antagonist. This investigational drug product has been designated with the name "AXS-05," and for clarity, we will refer to it as such in this protocol. In three completed Phase I trials and two ongoing Phase II/III trials sponsored by Axsome, AXS-05 has been found to be generally safe and well-tolerated in the completed three Phase 1 studies and the adverse event profile of AXS-05 was similar to that of BUP alone. AXS-05 is currently being evaluated for efficacy and safety in "adequate and well-controlled registration trials in treatment-resistant depression and agitation associated with Alzheimer's disease (see below). Thus far, AXS-05 has not been tested for its effect on tobacco use in humans; furthermore, to our knowledge, DXM has not been studied in combination with BUP or any other CYP2D6 inhibitor (e.g. quinidine) for its impact on tobacco use in humans.

2. The disease population: This study evaluates individuals with tobacco dependence. Tobacco use is the number one cause of preventable morbidity and mortality in the US[1,2]. It causes 480,000 deaths per year and is the cause of death in approximately two-thirds of all smokers[2].

3. The clinically unmet need for this type of supportive care: Pharmacotherapy is the primary treatment used by people who smoke to quit smoking. Approximately 29.9% of all smokers attempt to quit smoking with the use of a

medication[3]. Currently, there are seven FDA approved smoking cessation medications: varenicline, bupropion, nicotine patch, gum, lozenge, inhaler, and nasal spray[4]. These FDA approved medications roughly double the chances of quitting during any given quit attempt; efficacy vs. placebo of RR=1.7 (nicotine gum), RR=1.8 (bupropion) to RR=2.4 (varenicline)[5]. Development of a new medication class with oral administration, low incidence of side effects, and greater efficacy than that of bupropion has the potential for high-level adoption and large-scale population impact.

4. Why the stated objectives of the research are important: This study is designed to produce evidence that AXS-05 leads to significant reduction in smoking compared to a matched dose of BUP through analysis of daily smoking diaries and leveraging the statistical advantages of repeated measures analysis. Additionally, the study is designed to assess measures which predict smoking abstinence: the 7 Day Smoking Abstinence Test [6]. The study is designed to closely monitor drug adherence through the diaries, assess side effects of medications, and assess the impact of urine drug levels on smoking behavior and side effects. Finally, an assessment of mechanism is provided to estimate the impacts of known physiologic activities. These inquiries are designed to demonstrate that AXS-05 has an impact on smoking behavior beyond that of BUP, a well-established and FDA approved tobacco dependence treatment. The study is designed to assess changes (reductions) in smoking behavior that may occur in current smokers who use AXS-05. If results are positive, the study outcomes are designed to guide further development of AXS-05 as a smoking cessation treatment.

5. The rationale for performing this research: The overarching rationale for performing this research is the study's high potential for future impact. If AXS-05 is found to be a safe and effective treatment and is approved as an aid to smoking cessation, it could be made available to thousands of smokers through Axsome's access to large-scale drug production and capacity for national distribution. This long-term potential for production and distribution means that positive study findings may lead to further development of this potential treatment and, if successful, a reduction in smoking rates in the US and abroad.

6. Citations for existing literature that supports the rationale for performing this research: Dextromethorphan Reduces Nicotine Self-Administration in Rats[7]. **Design:** Young adult female rats were fitted with jugular IV catheters and trained to self-administer a nicotine infusion dose of 0.03 mg/kg/infusion. Then, in a dose-effect function study, oral DXM was administered over five doses ranging from 0 to 30 mg/kg. **Results:** DXM administration significantly decreased nicotine self-administration in a dose-dependent manner with maximal effect seen at 30 mg/kg ($p<.0005$) (Figure 2). Throughout varied doses, motor function and food intake showed no significant changes, suggesting low toxicity. **Relevance:** This study showed that administration of DXM leads to decreased nicotine self-administration in rats, suggesting that we may observe a similar finding in humans if we are able to obtain similar plasma concentrations of DXM.

7. Published and unpublished clinical data, if any, that supports the conduct of this research: Studies completed by Axsome on AXS-05, described in the Investigators Brochure Version 4.0 [IND 129633] Section 5.1.1: AXS-05 (Bupropion and Dextromethorphan) Pharmacokinetics) provide evidence of the following: **1**. Administration of combination AXS-05 results in a significant increase in plasma DXM levels, **2**. BUP-inhibited metabolism of DXM extends DXM half-life sufficiently (from 2 hours to 20 hours) to allow for twice daily dosing of AXS-05 with stable plasma levels. Furthermore, additional studies, found that DXM co-administered with the metabolic inhibitor quinidine results in a reduction of depressive symptoms in patients with treatment-resistant depression[8] and DXM co-administered with the metabolic inhibitor quinidine results in reduction of agitation symptoms in individuals with Alzheimer's type dementia[9].

8. How conclusions derived from this research will be used: Results from this pilot study will be used as supporting evidence for the design of a fully powered, randomized controlled trial on the use of AXS-05 as a treatment for tobacco dependence.

9. Previous Human Experience with the Proposed Dose: The proposed doses to be used in this study are as follows: AXS-05 (105 mg BUP/45 mg DXM), twice daily and 105mg BUP SR, twice daily. The proposed dose of AXS-05 for this

study is identical to the dose used in Study AXS-05-301 during the six-week double-blind treatment period and used in Study AXS-05-AD-301 used for following the titration for five consecutive weeks (Days 8 to 43) (see Investigator's Brochure Version 4.0 [IND 129633] Section 5.5.1: AXS-05 (Bupropion and Dextromethorphan) Clinical Safety Experience). However, in the study, patients will be exposed to either AXS-05 or 105 mg BUP SR for only 28 days.

3.3. DESIGN AND PROCEDURE

Non-Treatment Study: This study is designed to assess changes in smoking behavior in smokers who use AXS-05 compared to those who use bupropion alone.

Research Design and Procedures Overview: The proposed study is a Phase II double-blind, randomized active-controlled 4-week trial of approximately 60 daily smokers willing to abstain from smoking for 1 week. We will consent up to 150 individuals and randomize up to 70 individuals into treatment arms. The goal is to achieve approximately 60 randomized participants that complete at least 3 weeks of assessments (assessments through Visit 4). Participants will be randomized with 1:1 allocation to AXS-05 (45 mg Immediate Release DXM + 105 mg Sustained Release BUP) vs. 105 mg Sustained Release BUP, twice daily (BID). Subjects will be instructed to only take 1 tablet for the first 3 days. Subjects not completing three weeks of assessments will be replaced to ensure that 60 randomized patients (30 per group) complete the study through the 3-week Follow-up Assessment Visit (Visit 4).

The dose of AXS-05 to be used in the study is identical to the one being used in the ongoing clinical trials in TRD and Agitation in patients with Alzheimer's Disease. DXM and BUP doses are FDA approved for other indications and have been found to be safe and generally well-tolerated in combination (as AXS-05) in three Phase I studies to date. Medications will be continued for four weeks in each group. Laboratory testing, including expired breath CO and salivary cotinine, will occur at the Baseline Visit and each visit thereafter to objectively assess the number of cigarettes smoked per day in addition to daily smoking diaries. Additional testing on smoking behavior will include abstinence testing during the 7-day Smoking Abstinence Test at the 4-week Follow-up Assessment Visit. Potential side effects of AXS-05 and BUP alone will be assessed through repeated survey administration with open-ended questions and spontaneous report. Adherence to drug use will be assessed through Medication Use Diaries collected at each study visit. Urine drug levels will be collected Visits 2-5 to allow for correlation of urine drug levels to the number of cigarettes smoked per day (Cotinine, CO) and side effects. Pre-post drug initiation changes in smoking urges, withdrawal, stress, depression, anxiety, motivation and sleep quality will be assessed as potential mediators of effect on smoking behavior.

3.4. SELECTION OF SUBJECTS

Inclusion Criteria:

1. Age 18 years or above
2. Daily smoker using 10 or more cigarettes per day[10]
3. Willing to be smoke-free for 7 days
4. Is able to provide written informed consent (in English) to participate in the study and able to understand the procedures and study requirements.
5. Is willing to voluntarily sign and date an informed consent form that is approved by an institutional review board before the conduct of any study procedure.
6. If female and of childbearing potential, is willing to use medically acceptable contraceptive measures for the duration of the study. Acceptable methods of contraception include (1) surgical sterilization (such as tubal ligation or hysterectomy, (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as rhythm method or Plan B ™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Exclusion Criteria:

1. Current use of a smoking cessation medication (e.g. nicotine replacement, varenicline, bupropion)
2. Current use of tobacco product other than cigarettes (e.g. e-cigarettes, smokeless tobacco)
3. Answer > 0 on suicidality question of Patient Health Questionnaire (PHQ-9) Depression Scale[11]
4. Active alcohol use disorder or hazardous drinking. This will be screened with the AUDIT-C, and positive scores (4 or greater for men and 3 or greater for women[12]) will result in study clinician assessment and discretion.
5. Use of illicit drugs in the last month (marijuana, cocaine, opiates, benzodiazepines, methamphetamine)
6. Severe symptomatic depression and or anxiety (study physician discretion)
7. Diagnosis of bipolar disorder, schizophrenia, PTSD and or adult ADHD
8. GAD-7 Anxiety scale of 15 or higher[13]
9. Chronic medical illness including diabetes with the use of insulin, Hemoglobin A1c > 7 (study physician discretion), heart disease diagnosed by angiogram, COPD diagnosed by pulmonary function testing and requiring an oxygen supply
10. Specific medications (Appendix 1)
11. Abnormal finding on physical exam (study physician discretion)
12. Expired breath carbon monoxide < 10
13. Abnormal EKG (study physician discretion)
14. Abnormal Complete Blood Count, Comprehensive Metabolic Panel, Urine Hgb AIC (study physician discretion)
15. Positive Urine Pregnancy Test (women of child bearing potential only) (QuickVue One Step hCG)[14]
16. Positive Urine Toxicology-5 Screen (methamphetamine, cocaine, opiates, benzodiazepines, THC)[15]
17. Contraindication to the use of bupropion including seizure disorder or conditions that increase the risk of seizure (including bulimia and/or anorexia nervosa, CNS tumor, severe stroke, abrupt withdrawal from benzodiazepines or alcohol).
18. Unstable hypertension (Blood pressure > 160/100)
19. Hepatic impairment as defined by ALT or AST levels greater than 2 times the upper limit of normal.

Use of Inclusion/Exclusion Criteria: The primary considerations for the use of inclusion/exclusion criteria include consent (English, age), patient safety (illness, medications, blood tests, pregnancy), and generalizability (willingness to quit, cigarette use, drug and alcohol use, psychiatric illness).

Assessment and Follow-up of Specific Exclusion Criteria:

If a participant is excluded based on criteria above, the study medical provider will further assess the exclusion through medical interview as needed. If this interview reveals a safety issue for the excluded individual, the medical provider will send a letter to the excluded individual's primary care provider or seek immediate medical assistance if necessary.

Management of specific exclusion criteria are detailed below:

Generalized Anxiety Disorder will be assess using the GAD-7[13]. Scores of 15 or higher indicate severe anxiety, and will be exclusionary. If a potential participant scores above a 15 they will be referred to their PCP for further follow-up. In

addition, the study Physician or PA will generate a letter to the excluded individuals PCP to notify them of the results. Suicidality will be assessed using the PHQ-9[11]. A score of >0 on question 9 of the PHQ-9 ("Thoughts that you would be better off dead or hurting yourself in some way") will be exclusionary. If a participant scores >0 on question 9, the Physician or PA will be notified immediately for further clinical assessment and appropriate referral and follow-up.

The Audit-C will be used to assess for alcohol use disorder[12] during the phone screen. A score of >4 for men or >3 for women will be considered positive, and the potential participant will be excluded from the study.

Bipolar Disorder will be assessed using the Mood Disorder Questionnaire (MDQ)[16]. A positive screen involves answering "Yes" to 7 or more of the 13 items in section 1, "Yes" to section 2, and "Moderate Problem" or "Serious Problem" in section 3. A positive screen will result in further assessment by the Physician or PA and appropriate referral and follow-up. If needed, the individual will be given information for the Duke Mental Health Services, including their phone number (919-684-0100).

Psychotic Disorders will be assessed using the Modified Mini Screen (MMS) Section C[17]. If the potential participant states "Yes" to any of the questions, or there is concern for psychotic disorder in the clinician's judgement, the potential participant will be excluded from the study. The study Physician or PA will assess for appropriate follow-up and referral. If needed, the individual will be given information for the Duke Mental Health Services, including their phone number (919-684-0100).

Anorexia and Bulimia will be assessed using the SCOFF Questionnaire[18]. An answer of "yes" to two or more questions will be considered a positive screen. A positive screen will result in further assessment by the Physician or PA and appropriate referral and follow-up. If needed, the participant will be given information for the Duke Center for Eating Disorders, including their phone number (919-668-0397).

A history of seizure disorder will be assessed through the Medical History form (Appendix 2) in two ways. First, participants will ask if they have a diagnosis of a seizure disorder. If the potential participant reports "Yes" to a diagnosis of seizure disorder, they will be excluded. Secondly, potential participants will be asked if they have ever experienced a seizure or seizure-like activity. If the individual reports "Yes," the study Physician or PA will further assess the event and provide additional follow-up and referrals as necessary. In addition, history of conditions that increase the risk for seizure will be assessed through the Medical History form (Appendix 2)

Potential participants will be assessed for medications that lower seizure threshold via a medication exclusion list, found in Appendix 1.

Assessment of Potential Side Effects throughout Study

During the course of the study, participants will be assessed at each visit on the following parameters to assess the potential for medication side effects: suicidality, psychosis, depression, anxiety, sleep quality, agitation, as well as an open-ended question on potential medication side effects.

Suicidality: A study drug, Bupropion, can increase the risk of suicidality, so suicidality will be assess at each study visit. Participants will be assess for suicidality using the PHQ-9 question 9 (Appendix 3) at each visit after initiation of the study drug. If a participant scores >0 on this question, the study clinician will administer the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS assesses suicidal ideation, intensity of ideation, and suicidal behavior. The results of the C-SSRS will be used for further clinical assessment and follow-up as needed. This follow-up will be based on a medical assessment of the situation, and may include a referral to mental health services or immediate psychiatric evaluation in the Emergency Department if needed.

Psychosis: Participants will be assessed for psychotic disorders using the MMS Section C (Appendix 20) at each visit after initiation of the study drug. If a participant answers "Yes" to any of the items on the MMS Section C, a study clinician will administer the Brief Psychiatric Rating Scale (BPRS) (Appendix 22). This will be used for further clinical assessment and follow-up as needed. The Brief Psychiatric Rating Scale (BPRS) is a clinician-administered instrument

used for assessing positive, negative and affective symptoms for psychotic disorders over 18 symptom constructs. A study drug, Bupropion, can cause psychosis, so this assessment will be used to assess for emerging or worsening symptoms of psychosis.

Depression: The Center for Epidemiologic Studies Depression Scale-Revised (CES-D-R) (Appendix 13) is a 20 item scale that asks participants to rate how often they have had symptoms of depression (following the DSM-V). A study drug, Bupropion, can cause depressive symptoms, so this assessment will be used to assess for emerging or worsening symptoms of depression. The score will be reviewed by the study clinician, and appropriate follow-up and referral will be initiated as needed.

Anxiety: The State-Trait Anxiety Inventory (STAI) (Appendix 12) is a 40 item introspective measure developed to assess both trait and state anxiety. A study drug, Bupropion, can cause anxiety, so this assessment will be used to assess for emerging or worsening symptoms of anxiety. The study clinician will review the results of the measure and arrange appropriate follow-up and referral as needed.

Sleep Quality: The Pittsburgh Sleep Quality Index (PSQI) (Appendix 15) is a 19-item scale that was designed to assess the quality and patterns of sleep of adults. A study drug, Bupropion, can cause sleep disturbance, so this assessment will be used to assess for worsening sleep quality. This measure will be administered at each study visit to assess for changes in sleep quality.

Agitation: The Brief Agitation Measure (Appendix 16) is a 3-item scale designed to assess a participant's agitation level. A study drug, Bupropion, can cause agitation, so this assessment will be used to assess for emerging or worsening symptoms of agitation. The study clinician will review this measure and provide further clinical assessment and follow-up as needed.

3.5. DURATION OF STUDY

TIMELINE: Study activities will occur over approximately 14-month period. Two and a half months are allocated for hiring and training staff, IRB approval, and development of procedures. Approximately nine months are allocated for recruitment of 150 consented subjects and enrollment of 670 subjects who smoke to achieve 60 randomized subjects who complete at least three weeks of assessment (Visit 4). Approximately one month is allocated to complete the Final Assessment Visits and approximately one and a half months are allocated for analyses and manuscript preparation (Table 1).

Table 1: Month Timeline for Grant-Funded Period

Study Activities	**14 Months**			
	Stage 1 2.5 months	**Stage 2 9 months**	**Stage 3 1 month**	**Stage 4 1.5 months**
Staff Hiring and Training				
IRB/Data Base Build				
Procedure Development				
Recruitment + Enrollment				
Assessment Visits				
Analysis and Publication				

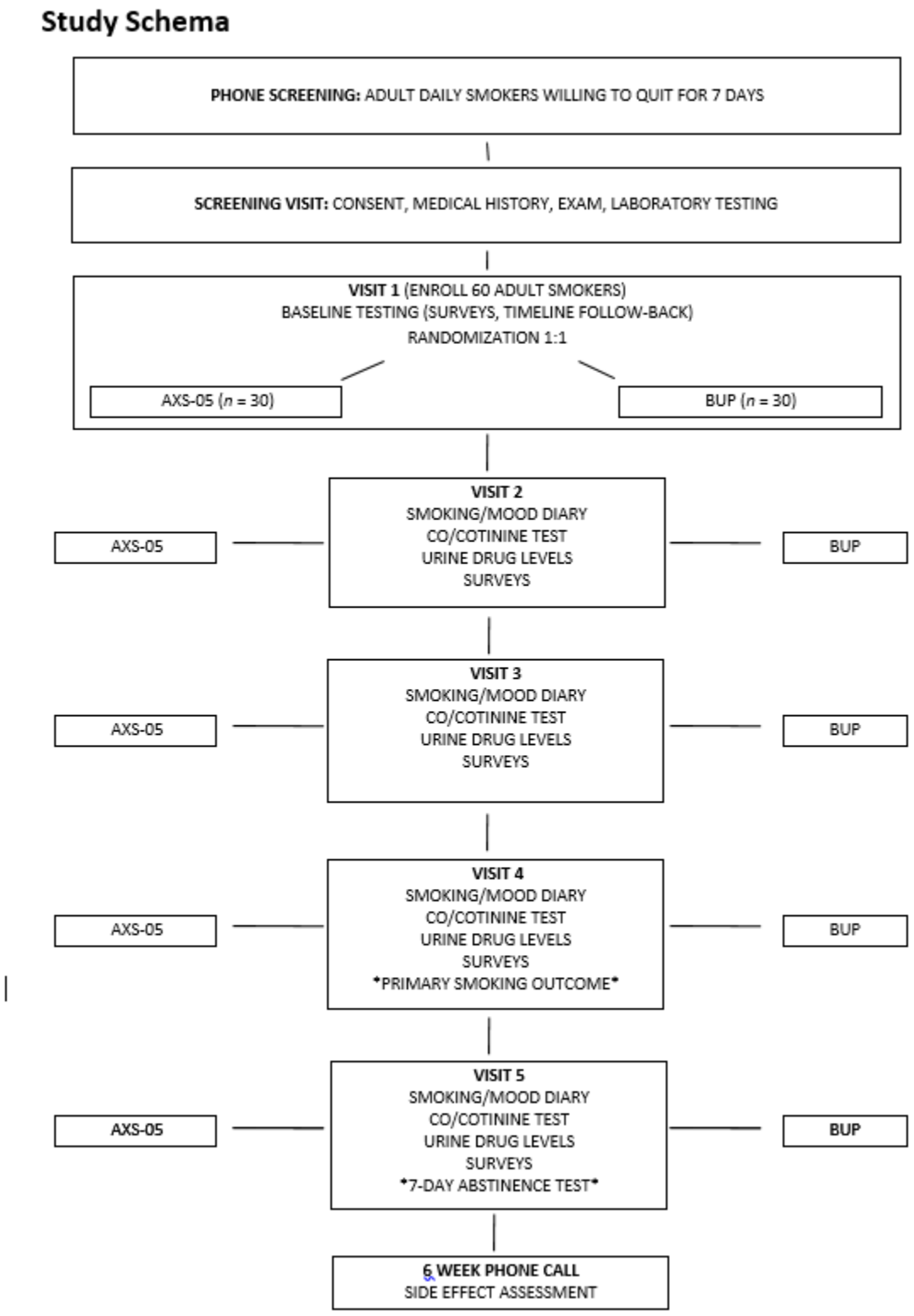
3.6. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A detailed Data Analysis is provided in Section 13. A summary of data analysis procedures includes the following: **Multilevel Modeling:** Given repeated observations across multiple individuals, many of the analyses in this study will be derived from multilevel modeling (MLM). **Missing Data:** Missing data will be examined to determine whether missingness is systematic (i.e. associated with individual baseline differences or time-related changes in observed variables). An intent-to-treat approach in which subjects lost to follow-up will be counted as non-abstinent will also be used to analyze univariate outcomes. An alpha criterion of 0.05 will be used in all comparisons. **Analysis of**

Primary Outcome: The primary study outcome is an assessment in change in smoking intensity from baseline to Week-3 Follow-Up Visit in AXS-05 vs. BUP groups with smoking intensity modeled as a latent variable through predictor variables of 1. Salivary Cotinine, 2. Carbon Monoxide Breath Test and 3. Number of cigarettes smoked per day. To enhance power for our primary outcomes, we will use repeated measures analysis to capture daily entry of the number of cigarettes smoked per day in smoking diaries. **Secondary abstinence outcomes**: Here we will include change in the number of cigarettes smoked per day from baseline to all Follow-up Visits (Visits 2-5), with confirmation of self-report through expired CO and salivary cotinine testing. We will also assess change in CO and cotinine as independent outcomes and abstinence rates through the 7 day Abstinence Test. **Assessment of potential moderators of primary effect:** The following constructs will be assessed as potential predictors of abstinence: demographics (age, gender, race, education), smoking history and heaviness, prior quit attempts, dependence (FTND), urge rating (MPSS), depression (PHQ-9), anxiety (GAD-7), alcohol use (AUDIT-C), drug use (DAST), stress (PSS-4), and self-efficacy questions. **Assessment of potential mediators of primary effect:** The following constructs will be assessed to determine whether assignment to the study group is associated with change pre- and post-treatment: urge rating (MPSS), depression (CES-D), anxiety (STAI), withdrawal symptoms (MNWS), stress (PSS-4), sleep quality (PSQI) and agitation (BAM).). **Sample Size Calculation:** Total sample size required to show differences in primary outcomes between AXS-05 vs. BUP with 10% downward adjustment in study group outcomes for possibility of unexpectedly poor outcomes is **N = 60 (completed patients). Approximately 66 subjects may be enrolled to achieve 60 randomized subjects who complete at least three weeks of assessments (Visit 4).**

All analyses will be performed on the Intent-to-Treat group that is defined as all subjects randomized and all replacement subjects, if applicable.

4. STUDY SCHEMA



5. BACKGROUND AND SIGNIFICANCE

5.1. STUDY CONDITION

1. Incidence, prevalence, and main causes and concerns:

Tobacco use is the number one cause of preventable morbidity and mortality in the US[1,2]. It causes 480,000 deaths per year and is the cause of death in approximately two-thirds of all people who smoke[2]. Since the 1964 Surgeon General's Report on the health effects of smoking[19], US smoking rates have fallen from 42.2%[19] to 15.1%[20]. Many smokers who have been able to quit, have already done so using available treatments. This means that today's remaining smokers who are unable to quit are an increasingly treatment-resistant population[4]. Abstinence rates for unassisted quit attempts are less than 5%[4] and new, successful treatment approaches for the current population of smokers are urgently needed.

2. The current therapeutic or management options:

Pharmacotherapy is the primary smoking cessation treatment used by people who smoke, with 29.9% of smokers attempting to quit smoking with the use of a medication[3]. Currently, there are seven FDA approved smoking cessation medications including varenicline, bupropion, nicotine patch, gum, lozenge, inhaler, and nasal spray[4]. These approved medications roughly double the chances of quitting during any given quit attempt; efficacy vs. placebo of RR=1.7 (nicotine gum), RR=1.8 (bupropion) to RR=2.4 (varenicline)[5]. Additionally, AXS-05 represents a new drug class with effects on depression and agitation (below) – constructs which are known to play a role maintaining tobacco use behavior. The development of a new class of drug which impacts tobacco use through reduction of depression symptoms and agitation has the potential to impact a large population of smokers who are unable to quit due to these affective challenges.

3. Explanation of how/why the current options are inadequate:

The relatively low dosing of BUP and DXM used in AXS-05 (DXM IR 45 mg/BUP SR 105mg) suggests the potential advent of a smoking cessation medication with a low side effect profile and high tolerability. Side effects strongly predict adherence to smoking cessation medications and are highly predictive of smoking cessation outcomes. In one study, smokers adherent to medication showed 1.8 times higher abstinence ($p = 0.0001$) than non-adherent smokers[21]. Unfortunately, the most commonly prescribed FDA approved smoking cessation medications (Varenicline and Nicotine Patch) have fairly high incidence of side effects (bupropion, nicotine lozenge and gum are better tolerated). One study comparing varenicline vs. placebo found the following side effect incidence rates: nausea (28.1% vs. 8.4%), headache (15.5% vs. 12.2%), vivid dreams (10.3% versus 5.5%)[22]. A meta-analysis[23] ($N > 177,000$) on side effects from nicotine replacement (the most commonly used smoking cessation medication) showed the following side effect rates vs. placebo (all $p < 0.001$): Headache (9.7% vs. 4.7), nausea (8.5% vs. 5.1%), insomnia (11.4% vs. 8.0%), skin irritation – patch (19.5% vs. 6.9%)[23]. A study ($N=225$)[24] on nicotine patch adherence (daily use for 28 days), found that 64.7% of participants were non-adherent and stopped regular use (30% forgot to use it, 15% had side effects, 10% relapsed, 7% financial challenges). A study ($N=662$) on nicotine gum adherence (use of 75% of prescribed gum) showed that 73.4% were non-adherent, most frequently due to forgetting to use the gum[25]. A study on Bupropion 150 mg SR showed that the side effects of insomnia, headache, and nausea are most common, but discontinuation of Bupropion 150 mg SR dosing due to side effects was only 7%[26]. Development of a new medication class with oral administration, efficacy beyond that of bupropion, and a low incidence of side effects has the potential for high-level adoption and large scale population impact.

4. Any relevant treatment issues or controversies:

AXS-05 has not been used for treatment of tobacco dependence. As such, there are no treatment issues or controversies that need to be explored. Because the drug is new for this indication, it is unknown whether the drug will lead to a reduction in smoking in humans. AXS-05 was found to be safe and generally well-tolerated in three Phase 1 trials conducted in over 100 subjects. To date, in two ongoing "adequate and well-controlled" clinical trials in

treatment resistant depression and agitation associated with dementia of the Alzheimer's type blinded study medication (AXS-05, BUP or placebo) has been well tolerated. Smoking is a behavior and there is no reason to think that side effects of AXS-05 will be different in smokers than those subjects enrolled in the three completed Phase 1 studies.

5. Other concerns related to quality of life or treatment deviation due to study condition:

AXS-05 is being used to reduce smoking behavior in current smokers. Smoking is a health hazard, and reduction in smoking is widely known to have health benefits. There is no treatment deviation due to study condition.

5.2. Study Drug

5.2.1. TYPE OF DRUG

AXS-05 as used in this study is a fixed-dose combination of dextromethorphan (DXM) immediate release (IR) 45 mg and bupropion (BUP) sustained release (SR) 105 mg taken two times daily. Either AXS-05 or BUP (SR) will be dosed twice daily (1 tablet for the first 3 days) for 28 days (4 weeks).

AXS-05 (AXS-05) (STUDY DRUG)

Information on drug structure, formulation, and manufacturing may be found within the Investigators Brochure Version 4.0 [IND 129633] Section 3: Chemistry and Pharmaceutical Information included in this application.

BUPROPION SR 105 mg (CONTROL DRUG)

Information on drug structure, formulation, and manufacturing may be found within Investigators Brochure Version 4.0 [IND 129633] Section 3: Chemistry and Pharmaceutical Information included in this application.

5.2.2. DRUG MECHANISM OF ACTION

Dextromethorphan Mechanism of Action:

DXM is a widely used over-the-counter cough suppressant with minimal side effects at recommended doses (5-15 mg every 2 hours or 30-60 mg twice per day)[27]. DXM easily crosses the blood-brain barrier[28]. In blood, 65% of DXM is bound to carrier proteins, with 35% of DXM in free form; a similar concentration of free DXM (30%) is found in urine and cerebral spinal fluid (CSF)[29]. Once DXM is in the CSF at sufficient concentrations, it binds to the following receptors: **α3β4 nicotinic acetylcholine receptor (nAChR)** is found in the presynaptic terminals of neo-cortical neurons that secrete norepinephrine as well as other sites[30,31]. DXM is an efficient α3β4 nAChR antagonist, acting independently of the nicotine binding site, providing robust (non-competitive) inhibition of the receptor[32]. The α3β4 nAChR and DXM binding of α3β4 nAChR are associated with reduction in physical withdrawal symptoms reduction in nicotine reward-based behavior[33, 34]; **Sigma-1 receptor** is found mostly within the cerebellum, brainstem, neocortex, striatum, and hippocampus[35]. DXM is a Sigma-1 agonist, as seen with cough suppression through binding of sigma-1 in the medullary cough center[36,37], but does not have significant activity at other opioid receptors[38,39]. Therapeutic effects of DXM activation of Sigma-1 include an anticonvulsant effect[37,40], significant neuroprotective effects in degenerative brain disease[41,42], and antidepressant effects in animals[43]; **N-methyl-D-aspartate (NMDA) receptors** are ligand-gated ion channels that, when activated, release glutamate (a fast acting excitatory neurotransmitter)[44]. DXM binds deep inside the NMDA ion channel as a non-

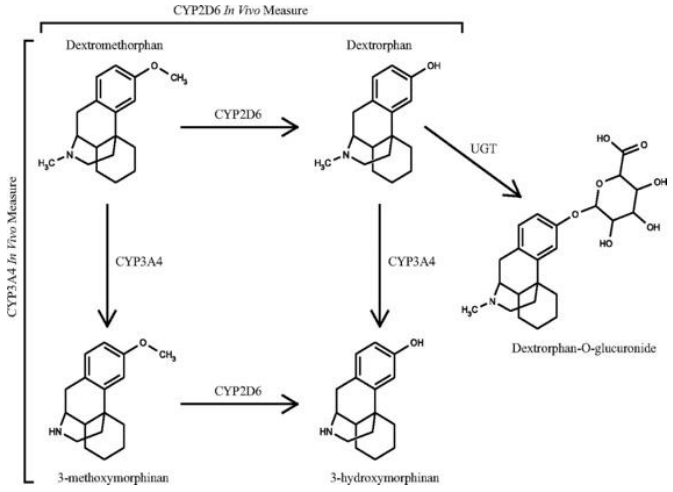


Figure 1: Dextromethorphan Mechanism of Action

competitive receptor antagonist[45]. Potentially important for addiction recovery, NMDA receptor activation is involved in neuroplasticity, and activates neurons involved in cue-based learning and memory formation[46,47,48]; **Serotonin** is a monoamine with substantial effect on regulation of mood in humans. Increasing synaptic serotonin by using a serotonin reuptake inhibitor is the primary mechanism of many antidepressants. There are 14 known serotonin transporters that control serotonin levels at various sites in the brain[49]. DXM is a non-selective serotonin transporter reuptake inhibitor (inhibits all known serotonin transporters) leading to increased serotonin levels in the brain[50] and co-administration of DXM and the metabolic inhibitor quinidine has previously been shown to reduce depressive symptoms in treatment resistant depression, agitation associated with Alzheimer's type dementia, and pseudobulbar affect (PBA); **Norepinephrine -** During nicotine withdrawal, an aspect of the withdrawal syndrome is related to low levels of synaptic norepinephrine[51]. Low norepinephrine is associated with poor attentional control, difficulty concentrating, and lack of productivity[52]. DXM is a norepinephrine reuptake inhibitor, and increases norepinephrine levels in the brain[53]. The following are DXM concentrations within the CSF required to activate each receptor: α3β4 nAChR = IC50 of 700nM[54]; Sigma-1 receptor = 400nM[53]; NMDA Concentrations of DXM necessary for NMDA blockade = 780 nM[55]. Serotonin receptors = 240 nM[56] norepinephrine (α1D receptor) 830 nM[29]. Unfortunately, DXM at FDA approved doses leads to CSF concentrations (4-600nM) that only activate Serotonin and Sigma-1 receptors, but not α3β4 nAChR, NMDA, or α1D, which appear to be critical to its role in reducing nicotine self-administration. Lower levels of DXM in the brain are a result of DXM metabolism (Figure 1)[57]. DXM is metabolized via the CYP2D6 pathway (Cytochrome p450) to dextrorphan. DXM metabolism occurs rapidly after ingestion during the first pass through the liver, resulting in roughly 95% of DXM being metabolized into dextrorphan. Dextrorphan does not easily pass the blood-brain barrier and shows minimal activity in the brain. One way to greatly increase the CSF concentration and central activity of DXM is to administer DXM with a CYP2D6 inhibitor. Bupropion is a potent CYP2D6 inhibitor at low (non-therapeutic) doses[58]. Interestingly, 5-10% of Caucasians have a homozygous deficiency of the CYP2D6 enzyme and metabolize DXM to Dextrorphan more slowly, showing higher CSF levels of DXM[59].

Bupropion Mechanism of Action:

Bupropion is an antidepressant medication that is FDA approved for use in smoking cessation under the trade name Zyban, referring to the 150 mg sustained release formulation taken two times daily. Bupropion is thought to help with nicotine dependence through several mechanisms. Bupropion is a selective norepinephrine and dopamine reuptake inhibitor that increases synaptic levels of norepinephrine and dopamine, but not synaptic levels of serotonin[60].

5.2.3. RATIONALE FOR USE OF STUDY DRUG IN THIS PARTICULAR SUPPORTIVE CARE CONTEXT

Rational for using combination AXS-05 in Human Smokers: AXS-05 has not been tested for its effect on tobacco use. AXS-05 shows considerable promise as a potential smoking cessation treatment of from a pharmacologic perspective of receptor binding. Additionally, AXS-05 is being evaluated in clinical trials for treatment-resistant depression and agitation associated with Alzheimer's type dementia and both depression and agitation have been shown to be associated with relapse in smokers. AXS-05 was safe and well-tolerated in 3 Phase 1 studies which enrolled over 100 subjects and a similar side effect to that of BUP alone. DXM has been shown to reduce nicotine self-administration in nicotine-dependent rats. Thus, it is reasonable to assess AXS-05 in smokers. If findings are positive, that is, if we see a significant reduction in smoking in AXS-05 vs. BUP alone, we will proceed with a fully powered, randomized smoking cessation trial on AXS-05 as a treatment for smokers who would like to quit smoking. If a fully powered smoking cessation trial were found to have positive results, Duke and Axsome would be well positioned to proceed with steps toward FDA approval of AXS-05 as a treatment for tobacco dependence.

The proposed dose and duration of use of AXS-05 for this study, is supported by other ongoing studies (Section 5.2.5 Clinical Experience).

5.2.4. PRE-CLINICAL EXPERIENCE OF STUDY DRUG

Pre-clinical experience (animal studies) have been conducted on DXM and BUP (the components of AXS-05). A description of these pre-clinical studies on DXM and BUP may be found within the Investigators Brochure Version 4.0 [IND 129633] Section 4: Nonclinical Studies included in this application. This includes information on non-clinical pharmacology, pharmacokinetics, toxicology, carcinogenicity, genetic toxicity, and reproductive and developmental toxicity.

Furthermore, a 2016 study at our center demonstrated that oral DXM administration significantly decreased nicotine self-administration of rats in a dose-dependent manner. Across the DXM dosing, which ranged from 0 to 30mg/kg, motor function and food intake did not show significant changes.

5.2.5. CLINICAL EXPERIENCE

Clinical experience with AXS-05 and with the control drug (BUP) may be found within the Investigators Brochure Version 4.0 [IND 129633] Section 5: Effects in Humans, included in this application. This includes information on human pharmacokinetics, distribution, metabolism, elimination, drug interactions, clinical efficacy, and clinical safety.

AXS-05 has been found to be safe and generally well-tolerated in three completed Phase 1 trials which enrolled over 100 healthy volunteers. In two ongoing blinded "adequate and well-controlled" clinical trials, blinded study medication was well tolerated (AXS-05, BUP or placebo). AXS-05 is being evaluated under IND124813 for treatment resistant depression (ClinicalTrials.gov Identifier: NCT02741791) and under IND129633 for Agitation associated with Alzheimer's Disease (ClinicalTrials.gov Identifier: NCT03226522).

5.3. STUDY PURPOSE/RATIONALE

1. Experience with similar supportive care therapies (in terms of efficacy and tolerability): This is the first time that AXS-05 has been studied in humans for the purpose of decreasing smoking. Other smoking cessation treatments have, however, made a dramatic impact on smoking. Abstinence rates for unassisted quit attempts are less than 5%[4], and new approaches to successful treatment of our current population of smokers are urgently needed. Pharmacotherapy is the primary treatment used by people who smoke to quit smoking, with 29.9% of smokers attempting to quit smoking with the use of a medication[3]. Currently, there are seven FDA approved smoking cessation medications including varenicline, bupropion, nicotine patch, gum, lozenge, inhaler, and nasal spray[4]. Approved medications vs. placebo roughly double the chances of quitting during any given quit attempt; efficacy vs. placebo of RR=1.7 (nicotine gum) to RR=2.4 (varenicline)[5]. Most of the medications used for smoking are moderately well tolerated. One study comparing varenicline vs. placebo found the following incidence rates: nausea (28.1% vs. 8.4%), headache (15.5% vs. 12.2%), vivid dreams (10.3% versus 5.5%)[22]. A meta-analysis[23] (N > 177,000) on side effects from nicotine replacement (the most commonly used smoking cessation medications) showed the following rates vs. placebo (all $p < 0.001$): Headache (9.7% vs. 4.7), nausea (8.5% vs. 5.1%), insomnia (11.4% vs. 8.0%), skin irritation – patch (19.5% vs. 6.9%), mouth soreness – gum/lozenge (5.4% vs. 2.9%)[23]. A study on (N=225)[24] nicotine patch adherence (daily use for 28 days), found that 64.7% of participants were non-adherent and stopped regular use (30% forgot to use it, 15% had side effects, 10% relapsed, 7% financial challenges). A study (N=662) on nicotine gum adherence (used of 75% of prescribed gum) showed that 73.4% were non-adherent, most frequently due to forgetting to use the gum[25]. A study on bupropion adherence (twice daily use x 6 weeks) showed non-adherence of only 37%[61]. Thus, most of the FDA approved smoking cessation medications, except perhaps bupropion, have significant associated side effects and problems with adherence for various reasons. Development of an orally administered medication (like bupropion) with a low incidence of side effects has the potential for comparatively high-level adherence and subsequently higher associated smoking abstinence rates.

2. Description of how the study therapy is different from current treatment paradigms, and how this difference might help meet an unmet supportive care need: The novel use of DXM for smoking cessation promises the potential approval of a new class of drugs in addition to current options for smoking cessation. The addition of

bupropion makes this drug safer and more effective by increasing CSF concentrations of DXM while decreasing total dose. Usefulness of this drug in smokers would potentially open the door to further exploration of drugs with effects on sigma-1, NMDA, or α3β4 nAChR.

3. What the potential benefits are for this supportive care intervention: This study is designed to produce evidence that AXS-05 (primarily DXM) is significantly more effective than bupropion alone at inducing a spontaneous reduction in smoking. Additionally, an assessment of mechanism is provided to estimate the impacts of known physiologic activities. Each of these inquiries is designed to guide future study in a fully powered trial through the Strategic Alliance funding mechanism. The study is promising because DXM has shown to reduce nicotine self-administration in animals and AXS-05 has a reasonable side effect profile in humans. The study also has a high potential for impact because AXS-05 could easily be made available to thousands of smokers due to an existing pharmaceutical infrastructure with large scale production and national distribution.

6. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary (1)	To evaluate the impact of AXS-05 compared to BUP on change in smoking intensity from baseline to the 3-Week Follow-Up Visit.	Number of cigarettes smoked per day will be assessed at baseline through smoking diary and at the 3-week Follow-up visit by smoking diary. Breath Carbon Monoxide testing will also be performed as well as saliva cotinine testing.	See Section 13.4
Key Secondary (2)	To compare AXS-05 to BUP on 7-day abstinence test between the 3 Week Follow-up and 4 Week Follow-up study visits.	7 day abstinence test starting at midnight of the 3 Week Study Visit and ending at the 4 Week Study Visit through self-reported smoking abstinence with biochemical confirmation using CO breath testing and salivary cotinine.	See Section 13.5
Key Secondary (3)	To assess potential baseline variables for an association with smoking behavior outcomes listed in objectives.	Potential predictors include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, and self-efficacy.	See Section 13.5
Key Secondary (4)	To compare AXS-05 to BUP on adherence to self-administered drug.	Adherence to self-administered drug will be measured via Medication Use Diaries completed by participants throughout the study and reviewed weekly at Study Visits.	See Section 13.5
Key Secondary (5)	To compare AXS-05 to BUP on tolerability through weekly, open-ended survey to assess potential side effects.	Tolerability of administered medications will be measured via weekly, open-ended surveys that collect information regarding potential side effects.	See Section 13.5
Key Secondary (6)	To compare AXS-05 to BUP on incidence of adverse events.	The incidence of adverse events or serious adverse events will be assessed utilizing FDA accepted reporting guidelines on these outcomes.	See Section 13.5
Key Secondary (7)	To measure urine drug levels of DXM at weeks 1-4 and assess potential correlation of these levels with smoking behavior and side effects.	Urine drug levels of dextromethorphan will be measured at baseline and all four time points with correlation assessed between urine DXM at each time point and smoking behavior across all study participants and across individual cohorts.	See Section 13.5
Key Secondary (8)	To compare AXS-05 to BUP on changes from baseline vs. weeks 1-4 Follow-up visits on the following: smoking urges, withdrawal symptoms, smoking reward, stress, anxiety, depression, self-efficacy, sleep disturbance, agitation, and emotion regulation.	Changes in smoking urges and withdrawal symptoms, stress, anxiety, depression, sleep quality and self-efficacy will be assessed by self-report at baseline vs. all four Follow-up Visit time points.	See Section 13.5
Key Secondary (9)	To compare AXS-05 to BUP on change from baseline to weeks 1-4 on daily assessment of the following: urge frequency, urge severity, and irritability.	Smoking urges and mood irritability will be assessed via daily entries in diary reports.	See Section 13.5

7. INVESTIGATIONAL PLAN

7.1. STUDY DESIGN

1. Specifics about study type: The proposed study is a double-blind, randomized active -controlled 4-week trial of 60 daily smokers attempting to quit. Up to 150 individuals will be consented with up to 70 individuals being randomized. The main goal is to have 60 randomized smokers' complete assessments at study visit 4. Smokers will be randomized with 1:1 allocation to AXS-05 (45 mg Immediate Release DXM + 105 mg Sustained Release BUP) vs. 105 mg Sustained Release BUP. Medications will be dosed twice daily (1 tablet for first 3 days) and continued for four weeks in each group with laboratory testing at baseline and then once per week to assess the number of cigarettes smoked per day with objective confirmation through assessment of expired breath carbon monoxide (CO) and salivary cotinine. Additional testing on smoking behavior will include abstinence testing during a 7-day abstinence test (starting at midnight after the 3-Week Follow-up Study Visit and ending at the 4-Week Follow-up Study Visit). Potential drug side effects will be assessed through repeated survey administration and spontaneous report. Adherence to drug use will be assessed through Medication Use diaries. Urine drug levels will be collected at Week 1-4 Follow up Visits to allow for correlation of urine drug levels to the number of cigarettes smoked per day (Cotinine, CO) and side effects. Because DXM and BUP have independently been shown to impact smoking urges, withdrawal, stress, depression, and anxiety, changes in these psychiatric variables will be assessed throughout the trial and evaluated as potential mediators of effect on smoking behavior.

2. Design and supporting rationale:

Selection of Subjects

Recruitment: Subjects will be recruited through the Duke Center for Smoking Cessation (CSC) using standard recruitment procedures including television, radio, web-based (ex: Facebook, Instagram, Craigslist, JobFinder, StudyKik, etc.), print-based media (ex: JobFinder, etc.), and flyers. All ads will feature a phone number and contact email for potential participants and can be found in the Recruitment section on eIRB. This study will also recruit participants through the Duke Primary Care Research Consortium (PCRC). Patients will be contacted through the Duke PCRC and scheduled for appointments with study personnel at the CSC. Authorization has been provided by the DPC Research Consortium, which will provide access to smokers who have consented to be contacted for research. The Research Consortium manages multiple studies to avoid conflict between studies and will provide access to a few DPC Clinics. DPC includes a network of 40 primary care clinics throughout Duke University Health System. Patients who attend visits with DPC medical providers at within Duke Primary Care are screened to see if they are willing to be contacted to find out about available research. DPC patients who are identified within the Electronic Health Record as being "current smokers" will be available for contact for our study. Using a regularly generated report, research staff will mail these patients letters from their medical providers that describe the study. The letter will also include a phone number if the patient does not want to be contacted about the study. Research staff will call the patients that do not opt-out and describe the study. If they are interested and meet inclusion criteria, the research staff will schedule them for a screening visit at the Duke Center for Smoking Cessation (CSC) (central study site). In addition, participants will be recruited using IRB-approved flyers placed around the Triangle Area (Durham, Raleigh and Chapel Hill). Examples of locations where flyers may be placed include: grocery stores, churches, retail stores (ex: Walmart, Target, etc.), restaurants, banks, bus stops and gas stations. In addition, this study will recruit participants through the Digital Signage program occurring throughout DUH, Duke South Clinics, Duke Medicine Pavilion, Duke Cancer Center and other clinical facilities at Duke University Hospital. Digital signage will also be used in other locations throughout the Triangle Area (Durham, Raleigh and Chapel Hill). Futhermore, potential subjects will be recruited through pre-screen failures from other studies at the CSC. There are currently several studies recruiting smokers from communities in and around Durham, North Carolina through newspaper flyers, internet and TV advertisements, and word-of-mouth. If potential subjects fail to meet the pre-screening study requirements for these studies (Pro00072077, Pro00089760, Pro00042277) at the CSC, but are still interested in research, they will be routed to a CTA to be pre-screened for this study over the phone. If potential subjects meet the pre-screening study requirements and are still interested in participation, they will attend a physical screening session at the Duke CSC, located at 2424 Erwin Road, Suite 201, Durham, NC 27705. At the screening on-site visit, a CTA will meet with the patient in a private area of the CSC (consent

room) and provide the patient with the Study Consent Form for review. Finally, web-based recruitment methods will use a REDCap Survey that includes both the phone script as well as the screening questions. This survey will allow participants to complete the phone consent process immediately. Incoming survey responses will be reviewed by a Technician at the Duke Center for Smoking Cessation (CSC). Potential participants who pass the phone consent will be called after review to schedule a screening visit. Potential participants may also be called if survey responses require additional review or clarification. Survey responders who do not qualify for the study will not be called.
CSC subject recruitment in the past has shown demographic distribution outlined in Table 2. We will recruit smokers into this study who state that they are willing to attempt to quit smoking for at least 7 days. Evaluation of this population should allow for an unencumbered assessment of pharmacological effects of the drug on smoking behavior.

Table 2: Duke Center for Smoking Cessation Recruitment Population

Female	51.1%
Mean Age	46.3
White	49.2%
Black	44.9%
Educ. > high school	48.4%
Mental Illness	30.5%

Planned number of subjects: A total of approximately 120 subjects will be consented with 66 subjects being randomized and enrolled with the goal of having 60 randomized subjects (30 per arm) complete assessments through study visit 4. With expected attrition of 10% between enrollment and study completion, we expect to enroll approximately 66 participants to obtain 60 completers (completer is defined as having completed assessments through study visit 4).

Randomization: Subjects will be randomized with stratification by Fagerstrom Test for Nicotine Dependence score (assessment of nicotine dependence) and gender to ensure roughly equal distribution of these characteristics between the two groups.

Phone Screening, Screening Visit, and Informed Consent: People who smoke who call in to the CSC will be screened by phone by a Clinical Research Specialist. If they pass phone-screening criteria, they will be scheduled for a Screening Visit at the Duke Center for Smoking Cessation. At the Screening Visit, after obtaining informed consent and signing the Study Consent Form, they will complete several screening questionnaires (PHQ-9, GAD-7. FTND, MMS, MDQ, SCOFF), medical history and personal information forms, a physical exam, CO breath testing, EKG, blood test, urine drug screen, and urine pregnancy test (if applicable). If they pass criteria at the Screening Visit, they will be scheduled for the Baseline Assessment Visit. Patient will be assigned a unique screening number and a screening log will be maintained.

Baseline Assessment Visit: At the Baseline Assessment Visit, participants will perform CO breath testing, urine pregnancy test (if applicable), and a detailed review of systems. If cleared they will be enrolled in the study (assigned a Study ID enrollment number) and randomized to either AXS-05 (study group) or Bupropion (control group). Participants will then receive the Baseline Questionnaires (see below) as well as Baseline expired CO and urinary cotinine testing.**3. Drug Dose:** Subjects will be randomized with 1:1 allocation to AXS-05 (45 mg Immediate Release DXM + 105 mg Sustained Release BUP) vs. 105 mg Sustained Release BUP. Medications will be provided to participants at the Baseline Study Visit and continued for four weeks in each group.

Appointment Reminders: Participants will be provided with the option to receive text message appointment reminders. This is discussed at two different time points. At the Phone Screen, participants provide verbal consent via phone. If they pass the phone screen and are scheduled for their Screening Visit, participants are asked if they would

like to receive an appointment reminder via text. If the participant "opts in", then they are asked to confirm their phone number and cell phone provider. They will then be sent up to two different text message appointment reminders—three days prior and one day prior. Each message will ask them to reply to confirm their appointment. If they confirm, no more text messages are sent. If they are unable to attend, they are asked to call the Center for Smoking Cessation line to reschedule. Once the participant attends their Screening Visit, they are asked to sign the Adult Consent form, which will again ask if they would like to receive text message appointment reminders (in the same fashion as discussed above). Participants can opt out at any time but must verbally convey this request to research staff or submit it in writing. All standard messaging rates will apply to the participant. Messages will originate via Microsoft outlook, which has been approved by Duke University Health System Information Security. Participants will be informed that because text messaging does not provide a completely secure and confidential means of communication, please do not text message if you wish to communicate in private.

Study Group Dosing: Dextromethorphan Immediate Release 45mg + Bupropion Sustained Release 105 mg

Provided by Axsome as a single tablet containing both drugs

Dose Timing: For the first three days, take one tablet in the morning on an empty stomach (one hour prior to the morning meal or two hours after the morning meal). Thereafter take one tablet two times per day, on an empty stomach, at least 8 hours apart and 1 hour prior to a meal, or 2 hours after a meal.

Control Group: Bupropion Sustained Release 105 mg

Provided by Axsome as a single tablet

Dose Timing: For the first three days, take one tablet in the morning on an empty stomach (one hour prior to the morning meal or two hours after the morning meal). Thereafter take one tablet two times per day, on an empty stomach, at least 8 hours apart and 1 hour prior to a meal, or 2 hours after a meal.

Packaging of Medications: Bupropion provided to controls will be administered in such a way as to match study group medication appearance and schedule. The Clinical Trial Materials Manager will package all medications such that AXS-05 and Bupropion are packaged identically and research assistants interacting with patients are unaware of which drug is given.

4. Eligible subject population

For Inclusion and Exclusion Criteria please see this list on pages 9 and 10.

Use of Inclusion/Exclusion Criteria: The primary considerations for the use of inclusion/exclusion criteria include consent (English, age), patient safety (illness, medications, blood tests, pregnancy), and generalizability (willingness to quit, cigarette use, drug and alcohol use, psychiatric illness).

5. Number of subjects: Sample size will be N= 60 with pre-established randomization of numbers from 1-60 such that 30 are allocated to study group and 30 are allocated to controls. Participants who drop out and do not complete assessment through 3-week follow-up visit (Visit 4) will be replaced to reach a total of 60 study randomized completers and based on a 10% drop-out rate between enrollment and study completion, we are expecting to enroll approximately 70 subjects after having consented up to 150.

6. Number of centers: The study will be conducted at Duke Center for Smoking cessation (one site).

7. Treatment duration: The study treatment and assessment duration is provided in the table below. The study contains a Screening Visit followed by a Baseline Visit and four follow-up visits (Table 3 below).

8. Study Assessments: Study assessments are outlined in Table 3 and details are provided in full within the Appendices. All study visits (Visits 2, 3, 4, and 5) should be completed within +/- 5 days of the visit.

Table 3: Assessments and Assessment Visits

Assessments and Assessment Visits		Screen Visit	Baseline	1-week follow-up visit	2-week follow-up visit	3-week follow-up visit	4-week follow-up visit	6 week Phone Call
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Phone Call
Screening								
1	Screening Visit Checklist (Inclusion/Exclusion Criteria) (items above)	X	X*					
2.	Patient Health Questionnaire (PHQ-9) Depression[62]	X						
3.	Generalized Anxiety Diagnosis (GAD-7)[63]	X						
4.	Fagerstrom Test for Nicotine Dependence (FTND) (6 items)[64]	X						
5.	Modified Mini Screen (MMS)	X						
6.	Mood Disorder Questionnaire (MDQ)	X						
7.	SCOFF Questionnaire	X						
8.	Demographics Questionnaire	X						
9.	Contact Information	X						
10.	Medical History + Medications	X						
11.	Smoking History (non-standardized) (10 items)	X						
12.	Review of Systems (ROS)	X						
13.	Physical Exam	X						
14.	EKG	X						
15.	CBC, CMP, HgbA1C	X						
16.	Urine Drug Screen (5 item)[15]	X						
17.	Urine Pregnancy Test[14]	X	X					
18.	Screening Week Smoking Diary	X						
*An abbreviated evaluation of inclusion/exclusion criteria will be assessed at the baseline visit to provide the most up to date data prior to enrollment, including a urine pregnancy test.								

AIM1: Smoking Abstinence								
1.	Carbon Monoxide Breath Test[65]	X	X	X	X	X	X	
2.	Salivary Cotinine[66]		X	X	X	X	X	
3.	Recent Smoking Questionnaire (non-standardized) (4 items)		X	X	X	X	X	X
4.	7-Day Smoking Abstinence Test					X	X	
5.	6 week Phone Call Smoking Status Questions (2 Items)							X
AIM 2: Adherence and Tolerability								
1.	Smoking Diary			X	X	X	X	
2.	Urge and Irritability Diary			X	X	X	X	
3.	Medication Use Diary			X	X	X	X	
4.	Medication Side Effects Log[67]			X	X	X	X	
5.	End of Treatment Side Effects Questionnaire							X
6.	Urine testing for AXS-05 (DXM/BUP)			X	X	X	X	
7.	PHQ-9 question 9 + C-SSRS (suicidality assessment)*		X	X	X	X	X	X
8.	Modified Mini Screen (MMS) Section C + BPRS (psychosis assessment)*		X	X	X	X	X	X
AIM 3: Mechanism (nicotinic, affective and cue-based learning)								
1.	Mood and Physical Symptoms Scale (MPSS-2)[68]		X	X	X	X	X	
2.	Minnesota Nicotine Withdrawal Symptoms Scale (MNWS)[69]		X	X	X	X	X	
4.	State-Trait Anxiety Inventory (STAI) (40 items)[70]		X	X	X	X	X	
5.	Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) (20 items)[71]		X	X	X	X	X	
6.	Modified Cigarette Evaluation Questionnaire (mCEQ) (12 items)		X	X	X	X	X	
7.	Pittsburg Sleep Quality Index (PSQI) (10 items)		X	X	X	X	X	

8.	Brief Agitation Measure (3 items)		X	X	X	X	X	
9.	Perceived Stress Scale (PSS-4) (4 items)		X	X	X	X	X	

***** *If an enrolled participant scores greater than 0 on PHQ-9 question 9 (suicidality) they will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) with a clinician. If the participant answers "Yes" to any item on the MMS, they will complete the Brief Psychiatric Rating Scale (BPRS) with a clinician.*

Special Tests

7 Day Abstinence Test: At the Visit 4, subjects are asked not to smoke at all for the next 7 days. They will be paid an additional $70 to be abstinent[6]. Smoking abstinence will be tested in the 7 day abstinence test using self-reported total abstinence during the period with biochemical confirmation via expired carbon monoxide (CO) breath test < 7ppm (96.0% sensitivity and 93.3% specificity)[72] and salivary cotinine with a cutoff of < 13 ng/ml to define abstinence (sensitivity, 86.5%; specificity, 95.9%)[73].

Participant Compensation: Participants will receive the following compensation for attending visits and completion of various aspects of the study.

Screening Visit = $0

Baseline Visit (Visit 1) = $20

1 Week Follow-up Visit (Visit 2) = $30

2 Week Follow-up Visit (Visit 3) = $40

3 Week Follow-up Visit (Visit 4) = $50

4 Week Follow-up Visit (Visit 5) = $50

Smoking/Urges and Irritability Diaries = $120 ($30 per visit x 4 visits)

7 Day Abstinence Test = $70 (during week 4 visit only)

6 week Follow-Up Call= $0

With payments for various parts of completion the maximum possible a subject can obtain is the following:

Baseline Visit (Visit 1) = $20

1 Week Follow-up Visit (Visit 2) = $30 + $30 (diary) = $60

2 Week Follow-up Visit (Visit 3) = $40 + $30 (diary) = $70

3 Week Follow-up Visit (Visit 4) = $50 + $30 (diary) = $80

4 Week Follow-up Visit (Visit 5) = $50 + $30 (diary) + $70 (7-Day Abstinence Test) = $150

Total = $380

Use of ClinCards for compensation: Participants will be compensated using ClinCards to decrease attrition in the study. ClinCards are preloaded debit cards, on which credit can be added by study staff. This decreases the length of time until participants are compensated by several weeks and prevents participants from having to pay a check cashing fee. The Study Coordinator or Clinical Research Specialist will provide each participant with a ClinCard at the Baseline Visit and will add the compensation to the card. After approval by Travel & Reimbursement, the participant will have the money loaded onto the card.

7.1.1. DOSE MODIFICATION

If side effects from either of these drugs are observed and determined to be minor, the medication dosing in either group may be changed with the evening dose either moved earlier in the day or eliminated.

7.1.2. SAFETY CONSIDERATIONS

We plan to ask participants about the specific side effects which have been noted previously on AXS-05 at 105 mg BUP and 45 mg DXM (list provided in the Appendix 10). If participants are found to have any of these symptoms they will be assessed by the study physician or study medical provider to determine its severity, whether it may have been caused by the drug, and whether it requires dose adjustment or discontinuation of the drug.

7.1.3. MISSED DOSES

Missed doses of medications will not be replaced. There will be no "catch up" for missed doses. We will capture data on missed doses through the medication adherence diary.

7.1.4. CONCOMITANT MEDICATIONS/THERAPIES

A medication list is provided for medications which are contraindicated in the study (see Appendix 1). Participants will be asked to report the use of any new medications during the study, including medications containing Dextromethorphan. If new medications are started, the study physician or study medical provider will assess whether or not the participant must be removed from the study.

7.1.5. STUDY DRUG BLINDING

The study is double blinded such that participants, research assistants, and the study physician (each of whom have contact with participants) are unaware of group allocations. Pill bottles provided to participants will feature generic research labels (Medication X vs. Medication Z) through the Clinical Trial Materials (CTM) manager at the Duke Center for Smoking Cessation. The Clinical Research Coordinator (CRC), who oversees operations and has no contact with participants, will be aware of participant group allocation. Emergency un-blinding procedures are described in 11.3

7.1.6. RANDOMIZATION

Prior to the study start date, a stratified (gender and FTND score) randomization list will be generated through the REDCap Randomization Module[74] for a sample of 60 with 1:1 allocation to study and control groups via random permutation of integers without replacement[75]. The randomization list will be accessed sequentially as each participant is enrolled. Patients not completing three weeks of assessments (Visit 4) in this study will be replaced to previous randomized treatment group and will not be randomized.

7.2. RATIONALE FOR SELECTION OF DOSE, REGIMEN, AND TREATMENT DURATION

A dosing regimen of DXM IR 45 mg combined with BUP SR 105 mg, twice-a-day, is utilized in this study because of the following: 1) it is believed that sufficient and sustained levels of DXM in the CNS will be obtained and 2) there is preliminary evidence that the proposed dose of AXS-05 for 28 days will be safe based on the three completed Phase 1 studies and two ongoing Phase 2/3 studies in TRD and agitation in AD.

7.3. RATIONALE FOR CORRELATIVE STUDIES

No correlative study will be performed.

7.4. DEFINITION OF EVALUABLE SUBJECTS, ON STUDY, AND END OF STUDY

This study defines a subject as evaluable if they have completed 4 of the 5 study visits.

7.5. EARLY STUDY TERMINATION

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.6, which describes the procedure for prematurely withdrawn patients.

8. STUDY DRUG

8.1. NAMES, CLASSIFICATION, AND MECHANISM OF ACTION

AXS-05 (AXS-05) (STUDY DRUG)

Information on drug structure, formulation, and manufacturing may be found within the Investigators Brochure Version 4.0 [IND 129633] Section 3: Chemistry and Pharmaceutical Information included in this application.

BUPROPION SR 105 mg (CONTROL DRUG)

Information on drug structure, formulation, and manufacturing may be found within the Investigators Brochure Version 4.0 [IND 129633] Section 3: Chemistry and Pharmaceutical Information included in this application.

8.2. PACKAGING AND LABELING

Blinded study drug(s) will be provided in bottles to the CTM by Axsome. Axsome will ship AXS-05 and bupropion tablets in bottles identical to packaging used in prior studies. Bottles will be stored at Duke. Labels comprising the following information will be applied to each bottle: subject number, visit number, current year, "Duke Center for Smoking Cessation", IRB Protocol number, brief description of pack contents (with neutral language accounting for the blind/active-control), Center front desk phone number, and "For investigational use only" tag.

8.3. SUPPLY, RECEIPT, AND STORAGE

The Clinical Trial Materials (CTM) manager at the Duke Center for Smoking Cessation will be responsible for receiving, storing, and inventorying the study drug(s). All study drug(s) will be kept in a locked cabinet with thermometer inside, which will be checked weekly and recorded in a study temperature log. Active medications will be kept on separate shelves. The key to open the cabinet containing the study drug(s) will be kept in a separate drawer, which itself is locked by a second key which will be stored inside a key box in a hallway externally adjacent to the room containing the study drug(s).

8.4. DISPENSING AND PREPARATION

Study medication provided by Axsome (Section 8.2) will be dispensed by the CTM. Study technician(s) will "order" medications from the CTM Manager by sending an email when supplies for each respective medication group are running low. The CTM Manager and a deputized un-blinded second individual will conduct preparation of the study drug(s) according to both the order sent by study technician. Each order will consist of the preparation of anywhere from 12-16 new bottles. The CTM Manager and the second individual will review the prepared bottles to ensure that the full "order" has been met and then dispense the bottles to study technician(s) in advance of the relevant study visit(s). Details of the distribution of the bottles will be contained in a separate un-blinded study drug distribution sheet as well as within the blinded study medication dispensing log.

8.5. COMPLIANCE AND ACCOUNTABILITY

The CTM Manager will maintain an un-blinded inventory log only accessible to study team members who are not blinded, which will record date and amount dispensed of study drug(s) for every study visit, as well as the study and visit number. The log will contain a section that "counts" up and down the total inventory of each study drug as items are added and subtracted. Separately, a blinded inventory log will be co-maintained by the CTM Manager and study technician, which will detail for every study visit the: date/time ordered, date prepared, initials of individuals who conducted preparation, subject number, visit number, days of medication included, date received by study technician, initials of study technician who received study drugs, date dispensed to subject, date study drug(s) returned to the CTM Manager and the initials of study technician who returned study drugs to CTM Manager.

8.6. DISPOSAL AND DESTRUCTION

The CTM Manager will dispose of unused study drug(s) by placing into bins, which are collected by Stericycle (waste services) by contract for ultimate destruction.

9. ELIGIBILITY

For Inclusion and Exclusion Criteria please see this list on pages 9 and 10.

Use of Inclusion/Exclusion Criteria: The primary considerations for the use of inclusion/exclusion criteria include consent (English, age), patient safety (illness, medications, blood tests, pregnancy), and generalizability (willingness to quit, cigarette use, drug and alcohol use, psychiatric illness).

10. TRIAL PROCEDURES AND ASSESSMENTS

Overview of Assessments: Medications will be continued for four weeks in each group with laboratory testing at baseline and then once per week to assess the number of cigarettes smoked per day with objective confirmation via expired breath carbon monoxide (CO) and salivary cotinine at each visit. Additional testing on smoking behavior will include abstinence testing during a 1 week "practice quit" abstinence test (performed starting midnight after the 3 Week Follow-up visit). Potential drug side effects will be assessed through repeated survey administration and spontaneous report. Adherence to drug use will be assessed through Medication Use Diaries. Urine drug levels will be collected at Visits 2-5 to allow for correlation of urine drug levels to the number of cigarettes smoked per day (Cotinine, CO) and side effects. Because combination DXM and BUP have independently been shown to impact smoking urges, withdrawal, stress, depression, and anxiety, changes in these psychiatric variables will be assessed throughout the trial and evaluated as potential mediators of effect on smoking behavior. All study visits (Visits 2, 3, 4, and 5) should be completed within +/- 5 days of the scheduled visit.

Study assessments are outlined in Table 3 and details are provided in full within Appendix 3-16.

Special Tests

7-Day Smoking Abstinence Test: Starting at midnight after the 3 Week Follow-up Visit, subjects will be asked not to smoke at all for the following 7 days, and will be paid an additional $70 to be abstinent. Smoking abstinence will be tested in the 7 Day Abstinence Test using self-reported total abstinence during the period with biochemical confirmation via expired air carbon monoxide (CO) breath test < 7ppm (96.0% sensitivity and 93.3% specificity)[72] and salivary cotinine with a cutoff of < 13 ng/ml to define abstinence (sensitivity, 86.5%; specificity, 95.9%)[73].

10.1. SCREENING EXAMINATION

The screening examination will take place during the screening visit. Informed Consent will be signed by the participant before the physical exam and blood testing is performed. Subject data to be collected at the Screening Visit includes demographic information, contact information, medical history, smoking history, review of systems (ROS), as well as assessments for depression (PHQ-9), anxiety (GAD-7), nicotine dependence (FTND), psychotic and mood disorders (MMS and MDQ) and eating disorders (SCOFF). In addition, a physical exam, EKG, blood testing for CBC, CMP, A1C level, saliva testing for cotinine, urine drug screen, and urine pregnancy test will be done.

Phone Screening Procedures

The CRS will conduct phone screens to verify that potential subjects fit the basic inclusion criteria for this particular study. The CRS will be familiar with the IRB-approved study protocol, informed consent form, and phone script for the study. The CRS will be responsible for scheduling physical screens, documenting on the phone screen forms, and providing directions and appointment reminders for those callers that fit the inclusion criteria. Each potential subject will be given a brief description of the study to assess eligibility and interest. An IRB-approved phone script will be followed while conducting the phone screen. During the phone screen, the CRS will use the AUDIT-C (Appendix 28) as one way to verify if potential subjects fit the basic inclusion criteria. In addition, the CRS will ask potential subjects if they are willing to be smoke-free for 7 days. Each potential subject will be called up to three times and/or have three detailed messages left. If a subject is not contacted and a message is not left after two calls he/she will not be considered further for participation in the study. If the CRS leaves three messages for the potential subject and that subject does not call back, then no further attempts at contact will be made until the potential subject re-establishes contact. Participants will also be asked if they would like to receive text message reminders. If they opt in, phone number and cell phone carrier will be recorded. Participants will be informed that standard messaging rates will apply and be their responsibility. They can choose to opt out at any time. Two appointment reminders will be sent three days prior and one day prior and they will be asked to reply to confirm their appointment.

Once a subject has successfully completed the phone screening process and is eligible for a physical screening, the CRS will then schedule the appointment during the study Physician/Physician Assistant's specific work hours. The

physical screening appointments will be entered on the Outlook calendar; changes to appointments, such as cancellations and rescheduled visits should be documented on the calendar. It will be the responsibility of the CRS to check the calendar on a regular basis to ensure proper scheduling and preparation for these visits. The CRS should mail or e-mail an appointment notification letter and driving directions to the potential subject as soon as possible after completing the phone screen. If the subject does not want to provide a mailing address or e-mail address, then the CRS will be responsible for giving driving directions and instructions via telephone. The Preliminary Contact Form or a report containing the potential subject's preliminary phone contact data (if the phone screen is conducted using Access) will be completed by the CRS in anticipation of the Screening Visit.

Screening Visit Procedures

After granting their informed consent, potential subjects will be given the HIPAA Notice of Privacy Practices and sign an Acknowledgement of Receipt Form. They will also complete a demographics form (Appendix 25), contact information form (Appendix 26), medical history form and smoking history form. In addition, they will complete the ROS, PHQ-9, GAD-7, FTND, MMS, MDQ and SCOFF Questionnaire, and will have their blood pressure, pulse, weight, height, temperature, and expired air CO measured. Subjects will provide blood (maximum of 20mL for tests to measure general health), and urine for urinalysis and illicit drug testing. Women of childbearing potential will also have a urine pregnancy test. The study physician or PA will perform a physical examination and an EKG. The screening visit will last approximately two hours. They will be asked to complete a Cigarette Use Diary with the number of cigarettes they smoke from the day of the screening visit to Visit 1.

Blood and urine specimens will be sent to LabCorp for processing. The results of laboratory blood and urine tests will not routinely be given to participants to send or be sent to their physician to include in their medical record; however, if the subject's lab results are outside the acceptable range for participation in the study, the Physician/PA will send the subject a medical exclusion letter and a copy of the lab results. Participants who are accepted in the study but need medical follow-up due to minor abnormalities in lab results will also be informed by letter from the Physician/PA. A copy of the laboratory results will be included with the letter, which will also indicate that the condition does not interfere with his/her participation in the study. If the participant does not appear for the Screening Visit within 30 days of the screening phone call, the Preliminary Contact Form will be shredded.

10.2. TREATMENT PERIOD

Visit 1

The first study visit (also referred to as Baseline Visit) will take place approximately 1 week after the Screening Visit but no longer than 30 days after the Screening Visit. Subjects will provide a urine pregnancy test (if they are of child bearing potential) to provide greater assurance that this eligibility criteria has not changed. Subjects will complete baseline questionnaires and tests and will be randomized to AXS-05 or Bupropion. Baseline questionnaires include: Recent Smoking Questionnaire, MPSS-2, MNWS, PSS-4, STAI, CES-D, PSQI and mCEQ. Participants will also complete expired CO and salivary cotinine testing and have their blood pressure, heart rate and weight measured.

Subjects will initially be given a 12-day supply of study medications. This includes 7-days of medications to last until the next study visit (all study visits are 1 week apart) and an additional 5 days of medications to allow for the possibility of a missed visit and the need to reschedule within 5 days of the missed visit. Participants will receive verbal and written instructions on how to take them. At follow up visits, participants will be given enough medications so that their total supply allows for 1 week + 5 days in case of a missed visit. At the Week-3 Follow Up Visit (Visit 4), participants will be provided enough medication to continue to the final day of medication use. (Subjects will be called within three days after the first day of treatment to make sure the medications are being used as directed).

Subjects will also be given diaries to record medication use, irritability, urges, and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused

medications for proper disposal and compliance monitoring. Subjects will also complete a Medications Side Effects Log and discuss any side effects with Physician or PA at the next visit.

Visit 2 (1-Week Follow-up Visit)

The second visit (also referred to as 1 Week Follow-up visit) will take place approximately 1 week after Visit 1. Subjects will complete repeated questionnaires and tests. Repeated questionnaires include: Recent Smoking Questionnaire, PHQ-9 Question 9 and C-SSRS (if applicable), MMS Section C and BPRS (if applicable), MPSS-2, MNWS, PSS-4, STAI, CES-D, PSQI and mCEQ. Participants will also complete expired CO and salivary cotinine testing and have their blood pressure, heart rate and weight measured. Urine will also be collected to test for AXS-05. The CRC who is not blinded will handle the delivery of the urine samples to LabCorp. Only urine samples from those randomized into the AXS-05 arms will be sent to LabCorp for DXM testing. Because only study subjects and not controls will be tested for urine DXM, Lab Corp will be instructed to send urine DXM results to the attention of the CRC. The CRC will keep the results of the DXM testing private and secure so that blinded personnel do not see it. The CRC will make the urine DXM results available at the end of the study once the blind is removed.

Subjects will also complete a Medications Side Effects Log and discuss any side effects with Physician or PA at the next visit. Subjects will be given a supply of study medications to use for one week (+ 5 days in case of a missed visit).

Subjects will also be given diaries to record medication use, irritability, urges, and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. Participants will be asked to bring all remaining medications to every visit. Remaining medications will be reconciled with medication use data in participant diaries. Participants will be instructed not to “double dose” and not to take medications to “catch up,” but only to take medications at specified times (1 pill before breakfast and 1 pill before dinner). At the end of the study, any unused medications will be collected and destroyed.

Visit 3 (2-Week Follow-up Visit)

The third visit (also referred to as **(2 Week Follow-up Visit)**) will take place approximately one week after Visit 2. Subjects will complete repeated questionnaires and tests. Repeated questionnaires include: Recent Smoking Questionnaire, PHQ-9 Question 9 and C-SSRS (if applicable), MMS Section C and BPRS (if applicable), MPSS-2, MNWS, PSS-4, STAI, CES-D, PSQI and mCEQ. Participants will also complete expired CO and salivary cotinine testing and have their blood pressure, heart rate and weight measured.

Subjects will also complete a Medications Side Effects Log and discuss any side effects with Physician or PA at the next visit. Subjects will be given a supply of study medications to use for one week (+ 5 days in case of a missed visit).

Subjects will also be given diaries to record medication use, irritability, urges, and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring. Urine will also be collected to test for AXS-05. The CRC who is not blinded will be handling the delivery of the urine samples to LabCorp. Only urine samples from those randomized into the AXS-05 arms will be sent to LabCorp for DXM testing.

Visit 4 (3-Week Follow-up Visit)

The fourth visit (also referred to as **(3 Week Follow-up Visit)**) will take place approximately one week after Visit 3. Subjects will complete repeated questionnaires and tests. Repeated questionnaires include: Recent Smoking Questionnaire, PHQ-9 Question 9 and C-SSRS (if applicable), MMS Section C and BPRS (if applicable), MPSS-2, MNWS, PSS-4, STAI, CES-D, PSQI and mCEQ. Participants will also complete expired CO and salivary cotinine testing and have their blood pressure, heart rate and weight measured.

Subjects will also complete a Medications Side Effects Log and discuss any side effects with Physician or PA at the next visit. Subjects will be given a supply of study medications to use for one week (+5 days in case of missed visit).

Subjects will also be given diaries to record medication use, irritability, urges, and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring. Urine will also be collected to test for AXS-05. The CRC who is not blinded will be handling the delivery of the urine samples to LabCorp. Only urine samples from those randomized into the AXS-05 arms will be sent to LabCorp for DXM testing.

Starting at midnight of the day of Visit 4, Participants will receive instructions to not smoke over the following 7 days. Abstinence will be validated by self-report, expired CO, and salivary cotinine at Visit 5. If participants are self-report and biochemically validated as abstinent, they will receive an additional $70 in compensation at Visit 5.

Visit 5 (4-Week Follow-up Visit)

The fifth visit (also referred to as **4-Week Follow-up Visit)** will take place approximately one week after Visit 4. Subjects will complete repeated questionnaires and tests. Repeated questionnaires include: Recent Smoking Questionnaire, PHQ-9 Question 9 and C-SSRS (if applicable), MMS Section C and BPRS (if applicable), MPSS-2, MNWS, PSS-4, STAI, CES-D, PSQI and mCEQ. Participants will also complete expired CO and salivary cotinine testing and have their blood pressure, heart rate and weight measured. Urine will also be collected to test for AXS-05. The CRC who is not blinded will be handling the delivery of the urine samples to LabCorp. Only urine samples from those randomized into the AXS-05 arms will be sent to LabCorp for DXM testing.

Subjects will also complete a Medications Side Effects Log and discuss any side effects with Physician or PA at the 6-Week Phone Call.

6-Week Phone Call:

The 6-week Phone Call will take place approximately 2 weeks after the last scheduled study visit (Visit 5) for participants completing the study. If a participant drops out of the study early, this call will be placed approximately 2 weeks after the last study visit they attended. If the participant experiences an Adverse Event (AE), the call will be placed approximately 2 weeks after the resolution of the AE (whichever comes last). This call will occur by phone for all subjects. The purpose of this call is to assess the presence of any side effects following the end of treatment and current smoking status (Appendix 17, Appendix 29). At Visit 5 participants will be provided with the End of Treatment Follow-Up Side Effects Questionnaire (Appendix 17). At the 6-week Follow-up Phone Call, participants will be asked to review this questionnaire. They will also be asked to rate the severity of the side effect (1-not at all severe to 7-extremely severe) as well as its frequency (from “Just once” to “More than once a day”). If concerns arise during the phone call, the call will be transferred to the Study Physician/PA for management. In addition, the Study Physician/PA will review this questionnaire and contact the participant if there are concerns. An example of the End of Treatment Follow-Up Side Effects Questionnaire can be found in Appendix 17. Additionally, the subject will be asked to answer PHQ-9 Question 9 and if positive the C-SSRS assessment, as well as Section C of the Modified Mini Screen and if positive the BPRS assessment.

10.3. END OF TREATMENT

Visit 5, which is the 4-week Follow Up visit, will be the End of Treatment.

10.4. FOLLOW-UP PERIOD

After Visit 5, a 6 week follow-up phone call will occur. This follow-up, referred to as the “6-Week- Phone Call,” will take place approximately 2 weeks after the last scheduled study visit for participants completing the study, 2 weeks after participants who dropped out prior to study completion, or until all AEs are resolved (whichever comes later). This visit will occur over the phone for all subjects. Participants will be asked to return all unused medications at each visit. Participants who are concerned with side effects will be instructed to call the Center for Smoking Cessation. The CRS will report to the Physician/PA any reported side effects. Additionally, the subject will be asked to answer PHQ-9 Question 9 and if positive the C-SSRS assessment, as well as Section C of the Modified Mini Screen and if positive the

BPRS assessment. The follow up period for participants to call the study with side effects or other concerns will last for two weeks after Visit 5.

10.5. END OF STUDY

Study participation will end with each participant after the 6-Week Phone Call. If participants can not be reached by phone, they will be listed as "lost to follow-up" for purposes of analysis of results. If participants express interest in tobacco use treatment, a referral will be made to the Duke Smoking Cessation Program or other resources for further support. After all participants have completed the study, the study data collection period will be considered over and the team will begin analysis of results.

10.6. EARLY WITHDRAWAL OF SUBJECT(S)

10.6.1. CRITERIA FOR EARLY WITHDRAWAL

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Patient Compliance
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

10.6.2. FOLLOW-UP REQUIREMENTS FOR EARLY WITHDRAWAL

If a participant has cause for premature withdrawal, or if the PI decides that the participant should withdraw, he or she will be asked to attend a Premature Withdrawal Visit. If this occurs before Visit 5 (final treatment visit), the Premature Withdrawal Visit will essentially mirror Visit 5 (if the subject is able). At this visit all medication will be collected and no further medication will be dispensed to the participant.

10.6.3. REPLACEMENT OF EARLY WITHDRAWAL(S)

Subjects who withdraw, do not complete at least three weeks of assessments, or are lost to follow-up will be replaced in order to reach a total of N=60 randomized participants included in the analysis. It is anticipated that approximately 66 subjects will be enrolled into the study.

10.7. STUDY ASSESSMENTS

10.7.1. MEDICAL HISTORY

Medical history assessments will be completed by each subject. This assessment will include questions about any significant medical diagnoses, recent hospitalizations, surgeries, family history, social history, and medication use. Appendix 2 provides an overview of medical history information to be collected and is considered a baseline measure.

10.7.2. PHYSICAL EXAM

At the screening visit, a study physician or PA will conduct a physical exam of the participant for general health. Abnormal findings during the exam can be used to exclude participants from the study. An EKG will also be performed as part of the exam.

10.7.3. EXHALED CARBON MONOXIDE BREATH TEST

The Exhaled Carbon Monoxide Breath Test will be used as objective confirmation of participant-reported number of cigarettes smoked per day. Exhaled Carbon Monoxide Breath testing will be evaluated at Screening, Baseline, 1 week,

2 week, 3 week, and 4 week Follow Up Visits. Values less than 7 ppm are considered abstinent (96.0% sensitivity and 93.3% specificity).[72]

10.7.4. SALIVARY COTININE TEST

Salivary Cotinine test will be used as an additional objective confirmation of participant-reported number of cigarettes smoked per day. Salivary cotinine will be tested at the baseline, 1 week, 2 week, 3 week, and 4 week visits, with a cutoff of < 13 ng/ml to define abstinence (sensitivity, 86.5%; specificity, 95.9%)[73].

10.7.5. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

The Patient Health Questionnaire PHQ-9 for Depression (Appendix 3) will be used to screen for current (within 2 weeks) depression at the Screening Visit. Participants who have scores of zero or higher on question 9 (suicidality) will be excluded from the study[62]. Patients with severe and symptomatic depression may also be excluded based on physician/PA discretion.

10.7.6. GENERALIZED ANXIETY DISORDER (GAD-7)

Anxiety will be assessed using the GAD-7 (Appendix 4) at the Screening Visit. The measure will be used to exclude participants from the study who have severe symptomatic anxiety based on study physician/PA discretion[76].

10.7.7. SMOKING HISTORY

At the screening visit, the subject will complete the Smoking History questionnaire (Appendix 5). This non-standardized, 10-item questionnaire provides information on the number of pack years, social support, additional tobacco product use, and other drug use.

10.7.8. FAGERSTROM TEST FOR NICOTINE DEPENDENCE (FTND)

The FTND (Appendix 6) is a validated measure consisting of 6 items that assess a participant's level of physical nicotine dependence. The FTND will be administered at the Screening Visit.

10.7.9. RECENT SMOKING QUESTIONNAIRE

At the baseline, 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits a participant's recent smoking habits will be assessed using the Recent Smoking Questionnaire (Appendix 7). This non-standardized questionnaire provides information about the participants smoking behavior over the last 7 days.

10.7.10. SCREENING VISIT SMOKING DIARY

At the Screening Visit subjects will be given a diary (Appendix 8) to complete with the number of cigarettes smoked per day from the day of the screening until Visit 1. This will be used to establish baseline information on cigarettes smoked per day.

10.7.11. 7-DAY SMOKING CESSATION PROTOCOL

Subjects are asked not to smoke at all during a 7 day period between Visit 4 and 5. Smoking abstinence will be tested in this protocol using self-reported total abstinence with biochemical confirmation via expired air carbon monoxide (CO) breath test < 7ppm (96.0% sensitivity and 93.3% specificity)[72] and salivary cotinine with a cutoff of < 13 ng/ml to define abstinence (sensitivity, 86.5%; specificity, 95.9%)[73].

10.7.12. SMOKING, MEDICATION USE, URGE AND IRRITABILITY DIARY

Participants will be given a diary that will assess their cigarette use, medication adherence, urges, and irritability throughout the study. The diary will be given at the Baseline Visit and will be collected and reviewed at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. Any omissions will be reviewed with the participant by study staff and every effort will be made to obtain accurate and complete diary data. A sample diary can be found in Appendix 9.

10.7.13. MEDICATION SIDE EFFECTS QUESTIONNAIRE

Participants will be asked in-person at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits about any medication side effects they have been experiencing. Participants will also be asked about any side effects they have

been experiencing following the end of treatment at the 6-Week Phone Call. Participants will be asked if there are any side effects that they are experiencing. They will be asked to rate the severity of the side effect (1- not at all severe to 7-extremely severe) as well as its frequency (From "Just once" to "More than once a day"). The CRS as well as the Study Physician/PA will review this form. An example of the Medication Side Effects Questionnaire can be found in Appendix 10.

10.7.14. MOOD AND PHYSICAL SYMPTOMS SCALE (MPSS-2)

The Mood and Physical Symptoms Scale is a two question scale to assess urges to smoke over a 24 hour period. It will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The MPSS-2 can be found in Appendix 11.

10.7.15. STATE-TRAIT ANXIETY INVENTORY (STAI)[70]

The State-Trait Anxiety Inventory is a 40 item introspective measure developed to assess both trait and state anxiety. The STAI will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. These assessment time points will help assess overall levels of anxiety as well as situation-based anxiety. The STAI can be found in Appendix 12.

10.7.16. CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE-REVISED (CESD-R)[71]

The Center for Epidemiologic Studies Depression Scale-Revised is a 20 item scale that asks participants to rate how often they have had symptoms of depression (following the DSM-V). The scale will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The complete CES-D-R can be found in Appendix 13.

10.7.17. MINNESOTA NICOTINE WITHDRAWAL SCALE (MNWS)[69]

The Minnesota Nicotine Withdrawal Symptoms Scale is an 15 item scale that is designed to measure nicotine withdrawal symptoms (i.e. craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite or weight gain, depression, and insomnia). The MNSW will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The complete MNSW can be found in Appendix 14.

10.7.18. PITTSBURGH SLEEP QUALITY INDEX (PSQI)[77]

The Pittsburgh Sleep Quality Index is a 19 item scale that was designed to assess the quality and patterns of sleep of adults. The PSQI will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The PSQI can be found in Appendix 15.

10.7.19. BRIEF AGITATION MEASURE

The Brief Agitation Measure is a 3 item scale designed to assess a participants agitation level. Agitation is a common symptom of withdrawal, so will help assess overall experiences of withdrawal. The BAM will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The BAM can be found in Appendix 16.

10.7.20. MODIFIED MINI SCREEN (SECTION C)

The Modified Mini Screen is a 7-item scale designed to assess for psychotic disorders. Exclusionary criteria for this study includes people with a diagnosis of schizophrenia, so this measure will be used to evaluate eligibility for the study at the screening visit. In addition, the MMS (Section C) will be used at each study visit after initiation of the study drug to monitor for emerging psychosis, as Bupropion can precipitate neuropsychiatric conditions including psychosis. The MMS can be found in Appendix 20.

10.7.21. MOOD DISORDER QUESTIONNAIRE

The Mood Disorder Questionnaire is a 15-item scale designed to assess for Bipolar Disorder. Exclusionary criteria for this study includes people with a diagnosis of bipolar disorder, so this measure will be used to evaluate eligibility for the study at the screening visit. The MDQ can be found in Appendix 19.

10.7.22. SCOFF QUESTIONNAIRE

The SCOFF questionnaire is a 5-item scale designed to screen for eating disorders. Anorexia and Bulimia are contraindications to the use of Bupropion, so a diagnosis of these eating disorders will be exclusionary for this study. The SCOFF will be assessed at the screening visit, and can be found in Appendix 18.

10.7.23. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment. It assesses suicidal ideation, intensity of ideation, and suicidal behavior. Participants will be assess for suicidality using the PHQ-9 question 9 (Appendix 3) at each visit after initiation of the study drug. If a participant scores >0 on this question, the study clinician will immediately be contacted and the C-SSRS will be used for further clinical assessment and follow-up as needed. The C-SSRS can be found in Appendix 21.

10.7.24. BRIEF PSYCHIATRIC RATING SCALE (BPRS)

The Brief Psychiatric Rating Scale (BPRS) is a clinician-administered instrument used for assessing positive, negative and affective symptoms for psychotic disorders over 18 symptom constructs. Participants will be assessed for psychotic disorders using the MMS Section C (Appendix 20) at each visit after initiation of the study drug. If a participant answers “Yes” to any of the items on the MMS Section C, a study clinician will immediately be contacted and the BPRS will be used for further clinical assessment and follow-up as needed. The BPRS can be found in Appendix 22.

10.7.25. PERCEIVED STRESS SCALE (PSS-4)

The Perceived Stress Scale is a 4 item used to measure the perception of stress. Higher PSS scores have been associated with lower rates of smoking cessation. The scale will be administered at the 1 Week, 2 Week, 3 Week, and 4 Week Follow-up Visits. The PSS-4 can be found in Appendix 23.

10.7.26. MODIFIED CIGARETTE EVALUATION QUESTIONNAIRE (MCEQ)

The Modified Cigarette Evaluation Questionnaire (MCEQ) is a 12 item survey that assesses the rewarding and aversive effects of smoking. It will be administered at the 1 week, 2 week, 3 week and 4 week-follow-up visits. The mCEQ can be found in Appendix 24.

10.7.27. REVIEW OF SYSTEMS (ROS)

The Review of systems (ROS) is a list of possible symptoms covering the organ systems. The ROS will be administered at the screening visit as part of the medical evaluation to assess for any current symptoms a potential participant is experiencing. It can be found in Appendix 27.

10.7.28. AUDIT-C

Alcohol Use Disorders Identification Test-C is a three-item questionnaire used to screen for people with alcohol use disorders. A score of 4 or more for men or 3 or more for women will be considered positive, and will require physician discretion to determine if an active alcohol use disorder is present. If it is determined by a clinician that an active alcohol use disorder is present, the potential participant will be excluded from the study.. The AUDIT-C will be asked during the phone screen. It can be found in Appendix 28.

11. SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1. ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study therapy that may or may not be related to use of the study therapy. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject is randomized through the End of Study visit (as defined in Section 10.3), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

11.1.1. AES OF SPECIAL INTEREST

Adverse Events related to AXS-05 used in prior studies have been minimal and no SAEs have occurred. As such there are no adverse events, which will require special attention.

11.1.2. REPORTING OF AES

During each annual IRB review of the protocol, a list of all AEs will be provided to the IRB for review. This report includes whether the AE was likely related to study procedures, whether it impacted subject participation, whether the AE was resolved, and any other action taken.

11.2. SERIOUS ADVERSE EVENTS

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions

11.2.1. REPORTING OF SAES

Life-threatening (grade 4 or 5) SAEs, deaths, and unknown reactions or unexpected events that occur in the course of any patient's treatment of study (from the time of consent) or within 30 days following cessation of treatment are reportable. The DCI SAE Report Form and DCI Safety Review Form will be completed and submitted to the IRB per standard protocol. The initial report for each SAE or death should include at minimum the following information:

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred
- Description of SAE
- Description of patient's condition
- Indication whether the patient remains of study
- Causality or causal relationship

De-identified source documentation (i.e. discharge notes) must be sent with the SAE Report Form. Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible using the same forms mentioned above.

As soon as an investigator becomes aware of an AE that meets the definition of serious:

- The Study Coordinator will submit to Axsome Therapeutics or designee within 24 hours of Investigator's awareness, even if it is not felt to be drug related
- The investigator agrees to provide supplementary information requested by Axsome Therapeutics safety personnel or designee

SAEs will be reported by the PI in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office, NIDA, and FDA.

SAEs will be reported to the DUHS IRB using the following timelines:

- 24 hours – for an unanticipated study-related death
- 1 week (5 business days) – for an unanticipated problem that is a serious adverse event
- 2 weeks (10 business days) – for an unanticipated problem that does not meet the criteria of a serious adverse event

SAEs will be reported to the NIDA Serious Adverse Event Tracking and Reporting System (SAETRS) within 72 hours. The NIDA Program Official will be kept apprised of IRB actions related to SAEs and any plan to modify the protocol as a result of IRB recommendation will be subject to NIDA approval.

In accordance with applicable regulations, investigators will submit the SAE report to their local IRB according to local IRB institutional guidelines. Dr. Davis, the study PI is responsible for reporting the serious adverse event to the FDA in accordance with 21 CFR 312.32. Any SAE that is possibly related and unexpected will be reported to the FDA no later than 15 calendar days upon notification of the event. The FDA will be notified of any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after notification. This will be done by the study coordinator.

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) completed by the study coordinator/DCI.
- The final MedWatch Form must be submitted by the study site to Axsome within one to two business days of submission to the FDA.

11.3. EMERGENCY UN-BLINDING OF INVESTIGATIONAL TREATMENT

The Clinical Research Coordinator will not be blinded to the treatment. The Principle Investigator as well as the Clinical Research Specialist and statistician will be blinded. In the case that Emergency un-blinding is required, the

Principle Investigator will contact the Clinical Research Coordinator directly to obtain the necessary information. Emergency contact information for un-blinding will be the email and cell phone number of Leah Thomas, the study CRC: leah.thomas@duke.edu, 704-798-4498.

11.4. OTHER REPORTABLE INFORMATION

Other reportable information including pregnancy, development of disease, or hospitalization for non-study related causes will be reported as AEs or SAEs depending on the severity and assessed as to whether these are related to study procedures.

11.5. SPECIAL WARNINGS AND PRECAUTIONS

There are no special warnings or precautions for this study.

11.6. STOPPING RULES

The study will be stopped prior to its completion if: **1**. difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; **2**. any new information becomes available during the study that necessitates stopping the study; **3**. there are significant treatment related toxicities that become evident through the course of the study; or **4**. other situations occur that might warrant stopping the study.

11.7. SAFETY OVERSIGHT COMMITTEE (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities, and new information that may affect subject safety or efficacy. Annual safety reviews include but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analysis as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

11.8. EXTERNAL DATA AND SAFETY MONITORING BOARD (DSMB)

DSMBs are usually advised for Phase III multi-center clinical trials in which study participants are exposed to substantial risk or vulnerable populations are studied. This study, however, will be conducted at only one study site in Durham, North Carolina. Based on extensive clinical experience with bupropion and dextromethorphan as separate medications as well as recent trials on combined Dextromethorphan-Bupropion (AXS-05) demonstrating good medication tolerance and a favorable side effect profile, there is no reason to expect significant risks to subjects. Additionally, vulnerable populations will not be studied in this protocol. Hence, we have concluded that oversight by the scientific and medical team will be adequate for this study and that a formal DSMB will not be needed.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review, the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.
- DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan.

Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

12.2. AUDITS

The Duke School of Medicine Clinical Trials Quality Assurance (CTQA) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the CTQA auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

CTQA audits are designed to protect the rights and well-being of human research subjects. CTQA audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator-initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

CTQA audits examine research studies/clinical trials methodology, processes, and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.3. DATA MANAGEMENT AND PROCESSING

12.3.1. CASE REPORT FORMS (CRFS)

The electronic and paper CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff including the PI, PA, and CRS are permitted to make entries, changes, or corrections in the CRF.

Errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The PI or authorized key personnel will maintain a record of the changes and corrections.

An audit trail will be maintained automatically by the electronic CRF management system REDCap. Designated personnel will complete user training, as required or appropriate per regulations.

12.3.2. DATA MANAGEMENT PROCEDURES AND DATA VERIFICATION

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol. The PI, PA, and CRS will have access.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the CRC will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.3. STUDY CLOSURE

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

13. STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1. ANALYSIS SETS

Dataset will be collected through five visits: the Baseline Visit and four weekly study visits. Data will include information from self-report, diaries, and objective tests of urine, saliva, and expired CO. All data measures will be captured using REDCap[78], an encrypted, HIPAA compliant, data collection system. Data entry is time-stamped for use in calendar-based assessment visits with capacity for upload into statistical programs Excel, Statview, SAS, SPSS, MPlus, and R. Trained Duke staff will conduct data integrity processes for REDCap data[78].

13.2. PATIENT DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Participants will be adult smokers recruited through the Duke Center for Smoking Cessation

13.3. TREATMENTS

Drug Dose: Smokers will be randomized with 1:1 allocation to AXS-05 (45 mg Immediate Release DXM + 105 mg Sustained Release BUP) vs. 105 mg Sustained Release BUP. Medications will be provided to participants at the Baseline Study Visit and continued for four weeks in each group.

Study Group Dosing: Dextromethorphan Immediate Release 45mg + Bupropion Sustained Release 105 mg

Dose Timing Administration: For the first three days, take one tablet in the morning on an empty stomach (one hour prior to the morning meal or two hours after the morning meal). Thereafter take one tablet two times per day, on an empty stomach, at least 8 hours apart and 1 hour prior to a meal, or 2 hours after a meal.

Control Group: Bupropion Sustained Release 105 mg

Dose Timing Administration: For the first three days, take one tablet in the morning on an empty stomach (one hour prior to the morning meal or two hours after the morning meal). Thereafter take one tablet two times per day, on an empty stomach, at least 8 hours apart and 1 hour prior to a meal, or 2 hours after a meal.

13.4. PRIMARY OBJECTIVE

To evaluate the impact of AXS-05 compared to BUP on change in smoking intensity from baseline to the 3-Week Follow-Up Visit. Smoking intensity, refers to the total amount of smoke inhaled by the smoker and includes number of cigarettes smoked per day. Smoking intensity will be assessed as a latent variable modeled through three predictive factors: 1. Salivary cotinine which will be assessed at all study visits. 2. Expired carbon monoxide (CO) breath testing at all study visits and 3. Number of cigarettes smoked per day assessed via daily smoking diaries. Because salivary cotinine and CO are measured at weekly intervals, weekly means of cigarettes smoked per day will be calculated for each participant and used in the latent variable analysis.

13.4.1. VARIABLES

Cigarettes smoked per day, expired CO, salivary cotinine

13.4.2. STATISTICAL HYPOTHESIS, MODEL, AND METHOD OF ANALYSIS

Testing for our primary hypotheses will be based on use of smoking intensity as a latent variable constructed through modeling of 3 predictor variables – salivary cotinine, CO, and the number of cigarettes smoked per day. These variables will be assessed for the development of composite measure of smoking intensity through latent variable modeling. Modeling of primary outcomes in this way is expected to provide a more powerful and accurate assessment of smoking behavior by minimizing measurement error. Latent variable structure will be developed using established methods, with fit of the measurement model (i.e., latent variable) determined using standard fit criteria: standardized root mean square residual (SRMR) < .05, root mean square error of approximation (RMSEA) < .08, and

comparative fit index (CFI) > .90. The chi-squared test of model fit will also be consulted, with non-significance indicative of good model fit.

For some comparisons conducted in this study, logistic regression models will be assessed for computation of odds ratio (OR) estimates and confidence intervals (CIs). All analyses will follow an intent-to-treat approach with alpha criterion of 0.05 in comparisons. Given repeated observations across multiple individuals and time points, many of the analyses in this study will be derived from multilevel modeling (MLM). MLM hierarchically organizes data as a function of person-specific variables and time-point specific variables. Unlike repeated-measures ANOVA, MLM is able to handle data distributions with unequal variances across time points and individuals[79]. In addition to modeling between-person differences, MLM is also able to model within-person variability in variables that change over time. Because MLM procedures are based on maximum likelihood estimation and use all available data, MLM can accommodate missing data at random and is often considered favorable to multiple imputation techniques, which can yield varied results depending on the imputation model[80, 81].

Multilevel structural equation modeling (MSEM) will be used to test the primary hypothesis that participants in the study group will demonstrate decreased smoking intensity post-baseline relative to the control group. Specifically, the aforementioned smoking intensity latent variable will be modeled at the baseline, 1-week follow-up, 2-week follow-up, and 3-week follow-up as a function of treatment group and time of assessment, with the baseline assessment treated as the reference group. Treatment X Time interactions will additionally be explored to determine whether the two treatments are associated with distinct trajectories of smoking intensity. Linear contrasts within the context of the model will be derived to estimate point differences in smoking intensity between the treatment groups at the 3-week follow-up.

13.4.3. HANDLING OF MISSING VALUES, CENSORING, AND DISCONTINUATIONS

Missing data will be examined to determine whether missingness is systematic or at random. To manage the problem of random positive findings when making multiple comparisons[82, 83] (e.g. random significant findings occurring due to multiple proposed analyses), we will correct alpha by using the false discovery rate approach described by Glickman[84]. This methodology differentiates random findings from hypothesis-driven outcomes and is more powerful than Bonferroni-type alpha adjustments that control the false positive rate[79, 81, 82, 83, 85].

13.5. SECONDARY OBJECTIVES

Secondary Objectives (Smoking Behavior)

1. To compare AXS-05 to BUP on smoking abstinence within a 7-day Abstinence Test conducted between the 3-week and 4-Week Study Visits. Smoking Abstinence and approximate time of lapse will be assessed by self-report diaries and biochemically confirmed via expired CO and salivary cotinine.

Secondary Objectives (Covariates and Potential Moderators)

2. To assess specific baseline variables for an association with smoking behavior outcome, listed above. Baseline variables assessed will include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, and self-efficacy. If a baseline variable is found to be associated with change in smoking behavior, it will be treated as a covariate in a secondary analysis of smoking behavior and assessed as a potential moderator of treatment effect.

Secondary Objectives (Adherence, Side Effects, and Tolerance)

3. To compare AXS-05 to BUP on adherence to self-administered drug through Medication Use diaries
4. To compare AXS-05 to BUP on tolerability through weekly, open-ended survey to assess potential side effects.
5. To compare AXS-05 to BUP on the incidence of adverse events or serious adverse events utilizing FDA accepted reporting guidelines on these outcomes.

Secondary Objectives (Pharmacokinetics)

6. To measure urine drug levels of DXM at weeks 1-4 and assess potential associations of these levels with smoking behavior and side effects.

Secondary Objectives (Potential Mediators)

7. To compare AXS-05 to BUP on changes from baseline vs. weeks 1-4 Follow-up Visits on the following: smoking urges, withdrawal symptoms, smoking reward, stress, anxiety, depression, sleep disturbance, and agitation..
8. To compare AXS-05 to BUP on change from baseline to weeks 1-4 on daily assessment of the following: urge frequency, urge severity, and irritability.

13.5.1. KEY SECONDARY OBJECTIVE ANALYSIS

1. Participants allocated to AXS-05 vs. BUP alone will demonstrate a significantly higher abstinence rate during the 7 day abstinence test between the week 3 and week 4 Study Visits assessed via self-reported abstinence with biochemical confirmation using expired CO breath testing and salivary cotinine. Testing of this will be based on chi-square test of the difference in abstinence between AXS-05 and active with logistic regression used to compute odds ratio (OR) estimates and confidence intervals (CIs). Survival analysis of time to lapse as a function of treatment will be analyzed using Cox regression[86]. Participants who remain abstinent through the end of the 7-day Abstinence Test will be censored, meaning that a time of lapse is unavailable. Nevertheless, the number of censored participants per group will contribute to the respective hazard ratios estimated for each group. The proportional-hazards assumption (that the relative hazard of lapse will remain constant within each treatment group over time) will be tested via examination of Schoenfeld residuals[87]. It is hypothesized that participants receiving AXS-05 will be slower to lapse than participants receiving BUP.

13.5.2. OTHER SECONDARY OBJECTIVES

Secondary Hypotheses (Covariates):

1. Potential baseline predictors of tobacco use will not be associated with smoking behavior outcomes listed in objectives 1-6; these predictors include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, and self-efficacy (motivation). Logistic regression models will assess group differences in the change in smoking rates controlling for demographic variables (e.g., age, sex, race) and baseline covariates known to predict abstinence (e.g., nicotine dependence).

Secondary Hypotheses (Adherence, Side Effects, and Tolerance)

2. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference on adherence to self-administered drug via Medication Use Diaries. This will be tested using non-inferiority testing through use of the two one-sided tests procedure (TOST) with determination of the equivalence margin, δ, with *f* of 0.50[88].
3. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference in spontaneous self-reported side effects. This will be tested using non-inferiority testing through use of the two one-sided tests procedure (TOST) with determination of the equivalence margin, δ, with *f* of 0.50[88].
4. Participants allocated to AXS-05 vs. BUP alone will demonstrate no significant difference on adverse events or serious adverse events utilizing FDA accepted reporting guidelines on these outcomes. This will be tested using non-inferiority testing through use of the two one-sided tests procedure (TOST) with determination of the equivalence margin, δ, with *f* of 0.50[88].

Secondary Hypotheses (Pharmacokinetics)

5. Participants allocated to AXS-05 vs. BUP alone will demonstrate the following with regard to urine drug levels at the two and three week visit:

A. Relatively stable urine drug levels of DXM (< 50% below or above the mean). This will be assessed using descriptive statistics.

B. A majority of participants will show urine DXM concentrations that are in the "expected therapeutic range" for tobacco dependence treatment (30 ng/ml). This will be assessed using descriptive statistics.

C. There will be an association between DXM levels and smoking behavior outcomes MSEM will be used to model the previously described smoking intensity latent variable at weeks 1-4 as a function of urine levels of DXM measured at those time points.

D. Urine levels of DXM will not be associated with a higher incidence side effects or adverse events (objectives 9-11). To examine the association of urine levels of DXM with side effects, number of days of reported side effects will be summarized at weeks 1-4 for each participant. These numbers will then be modeled (likely as a negative binomial distribution) via MLM as a function of urine levels of DXM. We will also examine whether urine levels of DXM that are above the sample mean will be associated with a higher incidence of side effects or adverse events.

Secondary Hypotheses (Potential Mediators)

6. In comparison to participants allocated to BUP, participants allocated to AXS-05 will demonstrate the following:
   A. A significant reduction in smoking urges and withdrawal symptoms from baseline to all four post-drug initiation time points. MLM will be used to model each of the above variables as a function of treatment group and time (baseline, weeks 1-4). Potential Treatment X Time effects will be explored to determine whether the two treatments are associated with distinct trajectories of change in the above outcomes. Linear contrasts within the context of the model will be derived to estimate point differences in the outcome variables between the treatment groups at the 3-week follow-up.

   B. The change in in smoking urges and withdrawal symptoms will be significantly associated with change in smoking behavior assessed through the primary objective, independent of treatment group. MSEM will be used to model the smoking intensity latent variable as a function of smoking urges and withdrawal symptoms, with treatment group and time (baseline, weeks 1-4) covaried. Potential Treatment X Time effects will be examined to determine whether the two treatments are associated with distinct trajectories of change in the behavioral and psychological outcomes. It is predicted that smoking urges and withdrawal symptoms will exert an effect on smoking intensity independent of treatment or Treatment X Time effects. Multicollinearity between each of the psychiatric variables will be examined and their independent effects as well as their joint effects will be tested. Pending evidence of mediation, indirect effects will be examined both independently and jointly. Multilevel analyses will be conducted using Mplus 7.

7. In comparison to participants allocated to BUP, participants allocated to AXS-05 will demonstrate the following:
   A. A significant reduction in stress, anxiety, depression, and withdrawal symptoms and an increase in self-efficacy and sleep quality from baseline to all four post-drug initiation time points. MLM will be used to model each of the above variables as a function of treatment group and time (baseline, weeks 1-4). Potential Treatment X Time effects will be explored to determine whether the two treatments are associated with distinct trajectories of change in the above outcomes. Linear contrasts within the context of the model will be derived to estimate point differences in the outcome variables between the treatment groups at the 3-week follow-up.

   B. The change in these constructs will be associated with change in smoking behavior assessed through the primary objective. MSEM will be used to model the smoking intensity latent variable as a function of the above potential mediators, with treatment group and time (baseline, weeks 1-4) covaried. Potential

Treatment X Time effects will be examined to determine whether the two treatments are associated with distinct trajectories of change in the behavioral and psychological outcomes. It is predicted that smoking urges and withdrawal symptoms will exert an effect on smoking intensity independent of treatment or Treatment X Time effects. Multicollinearity between each of the psychiatric variables will be examined and their independent effects as well as their joint effects will be tested. Pending evidence of mediation, indirect effects will be examined both independently and jointly. Multilevel analyses will be conducted using Mplus 7.

13.6. EXPLORATORY OBJECTIVES

There are no exploratory objectives.

13.6.1. KEY EXPLORATORY OBJECTIVE

N/A

13.6.2. OTHER EXPLORATORY OBJECTIVES

N/A

13.7. INTERIM ANALYSIS

Quality Control Analysis: We plan to conduct an interim analysis on de-identified data after a total of 10 subjects (5 in each group) complete Visit 5 (final visit) in the study. The study blind will not be broken for this analysis and as such it will not be known to which arm participants are allocated. This analysis will provide descriptive statistical assessments relevant to primary and secondary outcomes. This analysis will be conducted for the purpose of assessing the quality of our testing procedures, data collection, data storage etc. Because the study blind will not be broken, this analysis will not provide meaningful information on primary study outcomes. Data outcomes of this analysis will be shared with the PI but will not be shared with the funding agent (Axsome).

Efficacy Interim Analysis: Please see the additional attachment for the Statistical Analysis Plan (SAP). This will also be submitted to the FDA per normal procedures.

13.8. SAMPLE SIZE CALCULATION

This is the first time we know of that DXM has been used in a study on human smoking behavior. Thus, the effect size of AXS-05 vs. active control is unknown. Our primary outcome is defined as the number of cigarettes smoked per day assessed at the 3-week post drug initiation assessment visit. With 60 participants allocated to each arm of the study, we will have at a minimum 80% power to detect an effect equivalent to Cohen's d = 0.52. However, via the use of repeated-measures data, the proposed analysis will likely be sensitive to detect even smaller effects. The finding of spontaneous reduction of smoking period most closely parallels our finding of spontaneous reduction in nicotine self-administration in rats (who do not set a quit day or apply will power to bare on outcomes). Within the rat model, Dr. Ed Levin showed a reduction from 18 self-administrations to only 6 per day, a 66% reduction in use.

14. ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1. REGULATORY AND ETHICAL COMPLIANCE

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2. DUHS INSTITUTIONAL REVIEW BOARD AND DCI CANCER PROTOCOL COMMITTEE

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within one year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within one year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3. INFORMED CONSENT

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4. STUDY DOCUMENTATION

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (CRF) will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only approved study staff, including the Principle Investigator, Study Physician/PA, and Clinical Research Specialist are permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The Principal Investigator or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system (REDCap).

14.5. PRIVACY, CONFIDENTIALITY, AND DATA STORAGE

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database, REDCap, which is housed in an encrypted and password-protected Duke Server behind a firewall. Access to electronic databases will be limited to key personnel. Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6. DATA AND SAFETY MONITORING

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 11 (Sections 11.7 and 11.8 in particular) along with section 12.

14.7. PROTOCOL AMENDMENTS

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB and submitted to the IND prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB, FDA, and all other applicable regulatory agencies of such action immediately.

14.8. RECORDS RETENTION

The Principal Investigator will maintain study-related records for at least six years after study completion.

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15. APPENDICES

APPENDIX 1: Exclusionary Medication

The following medications are considered exclusionary if currently or recently being taken by a participant:

Abilify (aripiprazole)
Abiraterone Acetate
Adderall (dextro- & amphetamine)
Alosetron
Amantadine
Amitriptyline (Elavil, Endep)
Amoxapine (Asendin)
Anafranil (clomipramine)
Aripiprazole (Abilify)
Asenapine (Saphris)
Asendin (amoxapine)
Asunaprevir
Atomoxetine (Strattera)
Aventyl (nortriptyline)
Belviq (Lorcaserin)
Bontril (phendimetrazine)
Brexpiprazole (Rexulti)
Bromocriptine
Buproprion (Wellbutrin, Zyban)
Bystolic (Nebivolol)
Cabergoline
Carbamazepine (Tegretol)
Celexa (citalopram)
Chantix (Varenicline)
Cinacalcet
Citalopram (Celexa)
Clomipramine (Anafranil)
Clonidine
Clopidogrel (Plavix)
Clopress
Clozapine (Clozaril)
Cobicistat
Concerta (methylphenidate)
ConZip (Tramadol)
Coumadin (warfarin)

Dapoxetine (Priligy)
Darifenacin
Darunavir
Daytrana (methylphenidate)
DEP (Tenuate)
Desipramine (norpramin)
Desvenlafaxine
Desyrel (trazodone)
Detrol (Tolterodine)
Dexedrine (dextroamphetamine)
Dexmethylphenidate (Focallin)
Dextroamphetamine
Digoxin
Dolasetron
DOPamine
Dosulepin
Doxepin (Sinequan)
Duloxetine
Efavirenz (Sustiva)
Effexor (venlafaxine)
Elavil (amitriptyline)
Eldepryl (Selegiline)
Endep (amitriptyline)
Ergonovine
Ergotamine
Escitalopram
Fluoxetine (Prozac, Sarafem)
Fluphenazine (Prolixin)
Fluvoxamine (Luvox)
Focalin (dexmethylphenidate)
Geodon (ziprasidone)
Granisetron
Heparin
Imatinib

Imipramine (Tofranil, Tipramine, Norfranil)
Invega (paliperidone)
Isocarboxazid (Marplan)
Kaletra (Lopinavir)
Keppra (Levetiracetam)
Lacosamide (Vimpat)
Lamictal (lamotrigine)
Lamotrigine (Lamictal)
Latuda (lurasidone)
Levetiracetam (Keppra)
Levomethadyl
Levomilnacipran
Linezolid
Lisdexamfetamine(Vyvanase)
Lithium
Lofepramine
Lopinavir (Kalentra)
Lopressor (Metoprolol)
Lorcaserin (Belviq)
Lovenox
Ludiomil (Maprotiline)
Lumefantrine
Lurasidone (Latuda)
Luvox (fluvoxamine)
Maprotiline (Ludiomil)
Marplan (isocarboxazid)
Mellaril (Thiorizadine)
Metadate (methylphenidate)
Methylene Blue
Methylergonovine
Methylin (methylphenidate)
Methylphenidate (Ritalin, Concerta, Metadate, Daytrana, Methylin)
Metoclopramide (Reglan)
Metoprolol (Lopressor)

Midamor (AMILoride)
MiFEPRIStone (Mifeprex)
Mirabegron
Mirapex (pramiprexole)
Mirtazapine (Remeron)
Moclobemide
Namenda (Memantine)
Nardil (phenelzine)
Nebivolol (Bystolic)
Nefazadone (Serzone)
Nevirapine (Viramune)
Nilotinib
Norfranil (imipramine)
Norpramin (desipramine)
Nortriptyline (Aventyl, Pamelor)
Norvir (Ritonavir)
Olanzapine (Zyprexa)
Ondansetron
Oxaliplatin
Paliperidone (Invega)
Palonosestron
Pamelor (nortriptyline)
Panobinostat
Parecoxib
Parnate (tranylcypromine)
Paroxetine (Paxil)
Peginterferon Alfa-2B
Pergolide
Perhexiline
Phendimetrazine (Bontril)
Phenelzine (Nardil)
Phentermine
Pindolol
Plavix (clopidogrel)
Pramiprexole (Mirapex)
Priligy (dapoxetine)

Procainamide (Procanbid, Pronestyl)
Procarbazine
Prolixin (fluphenazine)
Promethazine
Propafenone (Rhythmol)
Protriptyline (Vivactil)
Qsymia (Phentermine + Topiramate)
Quetiapine
Quinidine
Quininet
Ramosetron
Rasagiline
Remeron (mirtazapine)
Rexulti (Brexpiprazole)
Rifampin (Rifadin)
Risperdal (risperidone)
Risperidone (Risperdal)
Ritalin (Methylphenidate)
Ritonavir (Norvir)
Rofecoxib (Vioxx)
Rolapitant
Ropinirole (Requip)
Rythmol SR
Safinamide
SAMe (S-adenosylmethionine)
Saphris (asenapine)
Sarafem (fluoxetine)
Selegiline
Seroquel
Sertraline
Sinequan (doxepin)
Soltamox (tamoxifen)
St John's Wort
Strattera (atomoxetine)

Surmontil (trimipramine)
Sustiva (Efavirenz)
Symbax (Fluoxetine / Olanzapine)
Symmetrel (amantadine)
Tamoxifen (soltamox)
Tasigna
Tedizolid
Tegretol (Carbamazepine)
Tenuate (DEP)
Tepadina
Terbinafine
Thioridazine
Thiotepa
Tipramine (imipramine)
Tipranavir
Tofranil (imipramine)
Tolterodine (Detrol)
Tranylcypromine (Parnate)
Trazodone (Desryl)
Trimipramine (Surmontil)
Tropisetron
Venlafaxine (Effexor)
Vilazodone (Viibryd)
Vimpat (lacosamide)
Viramune (Nevirapine)
Visken (pindolol)
Vivactil (protriptyline)
Vortioxetine (Trintellix)
Vyvanase (lisdexamfetamine)
Warfarin (Coumadin)
Wellbutrin (bupropion)
Zelapar
Ziprasidone (Geodon)
Zyban (bupropion)
Zyprexa (olanzapine)

The following medications will require the study clinician discretion to determine if they are exclusionary:

Acetaminophen (Tylenol)
Actiq®
Adenocard (Adenosine)
Alfenta®
Alfentanil
Almotriptan (Axert)
Alprazolam (Xanax)
Ambien (zolpidem)
Amerge (Naratriptan)
AMILoride
Amrix (Cyclobenzaprine)
Anexsia®
Aquachloral (chloral hydrate)
Ascomp® w/Codeine
Aspirin (ASA)
Astramorph™ PF
Ativan (lorazepam)
Avelox (Moxifloxacin)
Avinza®
Axert (Almotriptan)
Axid (Nizatidine)
B and O Supprettes®
Baclofen (Lioresal)
Balacet 325™
Bancap HC®
Baxdela (Delafloxicin)
Belladonna; Opium
Buprenomorphine
Buspar (buspirone)
Buspirone (Buspar)
Capital® with Codeine
Carisoprodol (Soma)
Celecoxib (Celebrex)
Ceta-Plus™
Cetraxal (Cipro)
Chloral Hydrate (Aquachloral,Somnote)
Chlordiazepoxide HCl (Librium)

Chlorzoxazone (Parafon Forte, Relax-DS)
Cimetidine
Ciprofloxacin (Cetraxal)
Clonazepam (Klonopin)
Codeine
Co-Gesic®
Combunox™
ComfortPak™
Cyclobenzaprine (Flexeril)
Dalmane (Flurazepam)
Damason-P®
Dantium (Dantrolene)
Dantrolene (Dantrium)
Darvocet
Darvon®
Delafloxicin (Baxdela)
Demerol®
DepoDur®
Diamorphine
Diazepam (Valium)
Dihydroergotamine
Dilaudid®
Dilaudid-HP®
Diphenoxylate
Dirame®
Diskets®
Ditropan (oxybutynin)
Dolagesic™
Dolophine®
Dolorex™ Forte
Duocet™
Duragesic®
Duramorph®
Eletriptan (Relpax)
Eloxatin (Oxaliplatin)
Endocet®
Endocodone®
Endodan®

Estazolam (ProSom)
Eszopiclone (Lunesta)
Eth-OxyDose™
Factive (Gemifloxacin)
Famotidine (Pepcid)
Fentanyl
Fentora™
Fioricet® with Codeine
Fiorinal® with Codeine
Fiortal® with Codeine
Flexeril (Cyclobenzaprine)
Floxin (Ofloxacin)
Flurazepam (Dalmane)
Frova (Frovatriptan)
Gabapentin (Neurontin, Horizant)
Gemifloxacin (Factive)
Glucophage (Metformin)
Halcion (triazolam)
Horizant (gabapentin)
Hycet™
Hycodan®
Hydrocet®
Hydrocodone
Hydrocodone; Ibuprofen
Hydrogesic™
Hydromet®
Hydromorphone
Hydropane®
Ibuprofen (Motrin, Advil)
Imitrex (Sumatriptan)
Infumorph®
Kadian®
Kava
Klonopin (clonazepam)
Levaquin
Levo-Dromoran®
Levo-Dromoran™
Levofloxacin

Levorphanol
Librium (chlordiazepoxide HCl)
Lomefloxacin
Lorazepam (Ativan)
Lorcet®
Lorcet® Plus
Lorcet®-HD
Lortab ASA®
Lortab®
Lunesta (eszopiclone)
Lyrica (pregabalin)
Margesic-H™
Maxalt (Rizatriptan)
Maxidone™
Memantine (Namenda)
Meperidine
Meperidine;
Meperitab™
Metaxolone (Skelaxin)
Metformin (Glucophage)
Methadone
Methadose®
Methocarbamol (Robaxin)
Milnacipran (Savella)
MorphiDex™
Morphine
Motofen®
Moxifloxacin (Avelox)
MS Contin®
MSIR®
Nalidixic Acid (NegGram)
Naltrexone
Naproxen, Napropsyn (Aleve)
Naratriptan (Amerge)
Narvox
NegGram (Nalidixic Acid)
Neurontin (gabapentin)
Nizatidine (Axid)
Norflex (Orphenadrine)
Norfloxacin
Noroxin

Nucynta (tapentadol)
Numorphan®
Ofloxacin
Opana®
Opana® ER
Opium Tincture
Oramorph®
Oramorph® SR
Orlaam®
Orphenadrine (Norflex)
Oxybutynin (Ditropan)
Oxycodone
Oxycodone; Naltrexone
OxyContin®
OxyFast®
OxyIR®
Oxymorphone
Oxytrex™
Palladone™
Panlor® DC
Panlor® SS
Paregoric, Camphorated Opium
Passionflower
Pepcid (Famotidine)
Percocet®
Percodan®
Percodan-Demi®
Percolone®
Perloxx
Phenco-Care™
Phrenilin® w/ Caffeine, Codeine
Pipemidic Acid
PP-Cap™
Pregabalin (Lyrica)
Propacet®
Propiram
Propoxyphene
ProSom (estazolam)
Prozac (fluoxetine)
Pyregesic-C™

Ralivia
Ranitidine
Relacore (contains passionflower)
Relafen
Remifentanil
Reprexain™
Requip (Ropinirole)
Restoril
Rizatriptan (Maxalt)
Robaxin (Methocarbamol)
Roxanol™
Roxicet®
Roxicodone®
Savella (milnacipran)
Skelaxin (Metaxalone)
Soma (Carisoprodol)
Soma® Compound w/ Codeine
Somnote (chloral hydrate)
Sparfloxacin
Stagesic®
Sublimaze®
Suboxone
Subutex
Sufenta®
Sufentanil
Sumatriptan (Imitrex)
Synalgos® DC
Tagamet HB
Tapentadol (Nucynta)
Temazepam
Tizanidine (Zanaflex)
Topamax (Topiramate)
Topiramate (Topamax)
Tramadol
Triazolam (Halcion)
Tylagesic™
Tylenol® with Codeine
Tylox®
TY-PAP with Codeine
Ultiva®

Ultracet	Vopac™	Zantac
Ultram	Xanax (alprazolam)	Zerlor
Valerian	Xodol	Zolpidem (Ambien)
Valium (diazepam)	Xodol 10/300	Zomig (Zolmatriptan)
Vicodin®	Zagam (sparfloxacin)	Zydone®
Vicoprofen®	Zanaflex (tizanidine)	

APPENDIX 2: Medical History

Major Medical Conditions:

Have you had any of the following conditions?

O Yes O No High blood pressure (Hypertension)

O Yes O No Heart attack OR heart disease diagnosis by coronary angiogram

O Yes O No Problems with heart valves such as regurgitation, stenosis, or artificial valve

O Yes O No Heart rhythm problem such as atrial fibrillation, tachycardia, or pacemaker

O Yes O No Heart failure requiring a diuretic (water pill)

O Yes O No Skin problems requiring medication

O Yes O No Liver cirrhosis (with jaundice or swollen abdomen)

O Yes O No Liver problems other than cirrhosis (e.g. hepatitis, fatty liver)

O Yes O No Kidney failure requiring dialysis

O Yes O No Chronic Kidney Disease not requiring dialysis

O Yes O No Chronic diarrhea due to Irritable Bowel Syndrome, Crohn's Disease, Inflammatory Bowel

O Yes O No Stomach/ Duodenal Ulcer (Gastrointestinal Ulcer)

O Yes O No Chronic Bronchitis (cough every morning)

O Yes O No Chronic Obstructive Pulmonary Disease (COPD) (Emphysema)

O Yes O No Asthma

O Yes O No Other chronic lung disorder such as Tuberculosis, Pulmonary Fibrosis, Sarcoid, or other

O Yes O No Stroke/ TIA (mini-stroke)

O Yes O No Seizure disorder

O Yes O No Regular headaches

O Yes O No Unexplained fainting spells

O Yes O No Insomnia requiring medications

O Yes O No Other neurologic conditions

O Yes O No Problems giving blood samples

O Yes O No Anemia requiring iron

O Yes O No Blood disorder

O Yes O No Rheumatic Disease such as Rheumatoid Arthritis, Fibromyalgia, or other

O Yes O No Sinusitis/ Seasonal allergies

O Yes O No Diabetes requiring insulin or other medications

O Yes O No Thyroid disease/ condition

○ Yes ○ No Cancer

○ Yes ○ No Depression/ Anxiety/ Bipolar disorder

○ Yes ○ No Suicidal ideation (thinking about ways to commit suicide) within the past year

○ Yes ○ No Suicide attempt during your lifetime

○ Yes ○ No Schizophrenia

○ Yes ○ No Post-Traumatic Stress Disorder (PTSD)

○ Yes ○ No Other Psychiatric problems (Borderline, Schizoaffective, Hypomania, ADHD)

○ Yes ○ No Chronic infections syndrome such as HIV, CMV, Epstein Barr

Please list any hospitalizations in the past 10 years. If possible, include the year:

1. _____ Year: _____
2. _____ Year: _____
3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

Please list any serious injuries or accidents. If possible, include the year:

1. _____ Year: _____
2. _____ Year: _____
3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

Please list any surgeries or major procedures. If possible, include the year:

1. _____ Year: _____
2. _____ Year: _____
3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

Women Only:

Date of last menstrual cycle: _____
Are you menstruating regularly? ○ Yes ○ No
Are you post menopausal (natural or from surgery)? ○ Yes ○ No

Are you willing to use medically acceptable contraceptive measures for the duration of the study?

Acceptable methods of contraception include (1) surgical sterilization (such as tubal ligation or hysterectomy, (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as rhythm method or Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

○ Yes ○ No

Family History

Has any first degree family member (child, parent, or sibling) had any of the following illnesses?

Illness	**Which family member?**
Anemia or Blood Disease	
Cancer	
Diabetes	
Heart Disease	
High Blood Pressure	
Severe Mental Illness	
Stroke	
Substance abuse (alcohol, tobacco, or other)	
Other serious illness	

Social History

Do you drink alcohol (e.g. beer, wine, liquor)? ○ **yes** ○ **no**

If YES, how many days per week do you have a drink containing alcohol? _____

How many drinks do you have on your heaviest drinking day of the week? _____

Do you currently drink coffee and / or tea? ○ **yes** ○ **no**

If YES, how many cups per day? _____

Have you used a non-prescription drug such as marijuana, cocaine or heroin in the last month? ○ **yes** ○ **no**

If YES, what drug / substance? _____

General Health

Do you use oxygen?

○ **no** ○ **yes, continuously** ○ **yes, for exertion or sleep**

Can you walk up 2 flights of stairs?

○ **no** ○ **yes, without stopping** ○ **yes, but I would need to stop along the way.**

How well do you walk?

○ **I walk independently** ○ **I walk with a cane** ○ **I walk with a walker** ○ **I use a wheelchair**

Have you ever experienced a seizure or seizure-like activity?

○ Yes ○No

Medications

Please list any medications you are allergic to:

1.	2.	3.

Please list all medications you are now taking or have used in the last month (include over-the-counter drugs, vitamins, and especially prescriptions). Ok to skip dates for long term medications:

Name of Medication	**Dosage**	**Start Date**	**Stop Date**	**Prescribed for what problem?**
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

Have you used experimental or investigational drugs in the past 30 days? ○ Yes ○ No

Smoking Cessation Medications

For each of the following, mark if you have used the medication, experienced any side effects, allergy or intolerance with usage, or had to stop taking the medication due to side effects:

	Not used	Used	Side Effects	Stopped due to Side Effects?	
				Yes	No
Nicotine Patch	○	○		○	○
Nicotine Gum	○	○		○	○
Nicotine Lozenge	○	○		○	○
Nicotine Inhaler	○	○		○	○
Zyban (Wellbutrin, Bupropion)	○	○		○	○
Chantix (Varenicline)	○	○		○	○

Have you used any of these medications in the past 30 days? ○ Yes ○ No

APPENDIX 3: Patient Health Questionnaire-9[89]

Over the past two weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3

Scoring

Depression Severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe.

APPENDIX 4: Generalized Anxiety Disorder 7-item Scale (GAD-7)[76]

Over the last 2 weeks, how often have you been bothered by any of the following problems?		Not at all	Several days	More than half the days	Nearly every day
1.	Feeling nervous, anxious or on edge	0	1	2	3
2.	Not being able to stop or control worrying	0	1	2	3
3.	Worrying too much about different things	0	1	2	3
4.	Trouble relaxing	0	1	2	3
5.	Being so restless that it is hard to sit still	0	1	2	3
6.	Becoming easily annoyed or irritable	0	1	2	3
7.	Feeling afraid as if something awful might happen	0	1	2	3

Calculate: Add scores of GAD-7 Responses together for total

0-5 = mild anxiety

6-10 = moderate anxiety

11 or above = high anxiety

APPENDIX 5: Smoking History Questionnaire

Please answer the following questions are about your history of smoking, use of other products and medications.

1. How many cigarettes have you smoked per day on average for most of your life?

_____ [1-99]

2. How many years have you smoked? _____ [1-99]

Calculate: number of cigs/day for most of your life (Q1)/20 x years smoked (Q2) – this will yield: "Pack Years" to be generated as an automatic input into the Specialist H+P. (Q1 is /20 because there are 20 cigs in a pack)

3. Do you usually smoke menthol or non-menthol cigarettes?
   - 1 = Non-Menthol
   - 2 = Menthol
   - 3 = Both
   - 0 = Don't know

4. Does your spouse/partner smoke?
   - 1 = YES
   - 2 = NO
   - 3 = Do not have a spouse/partner
   - 0 = Don't know

5. If you decided to quit, how likely would the people close to you support your decision to quit?
   - 1 = Not likely at all
   - 2 = Very unlikely
   - 3 = Somewhat unlikely
   - 4 = Neither likely nor unlikely
   - 5 = Somewhat likely
   - 6 = Very likely
   - 7 = Extremely likely
   - 0 = Don't know

6. How many times in your life have you stopped smoking for one day or longer because you were trying to quit smoking? _____ [0-99]

7. Have you used the following tobacco products in the last week? (Select all that apply)
   - 1 = Cigarettes
   - 2 = Cigars
   - 3 = Pipes

4 = Hookah
5 = Cigarillos
6 = E-cigarettes
7 = Chewing tobacco
8 = Orbs/sticks/sheets
9 = Snuff
10 = Other

8. During the last week did you use any of the following drugs? (Select all that apply)

0 = None
1 = Marijuana
2 = Cocaine/Crack
3 = Meth
4 = PCP
5 = Heroin
6 = Other

9. During the last week, did you use an opiate such as Codeine, Morphine, MS Contin, OxyContin, Oxycodone, Percocet, Hydrocodone, Vicodin, Hydromophone, Dilaudid, Duragesic or Fentanyl?

1 = Yes
2 = No
0 = Don't know

10. During the last week, did you use a benzodiazepine such as Lorazapam, Ativan, Valium, Alprazolam, Xanax, Clonazepam or Klonopin?

1 = Yes
2 = No
0 = Don't know

APPENDIX 6: Fagerström Test of Nicotine Dependence[64]

1. How soon after you wake up do you smoke your first cigarette?

    3= Within 5 minutes

    2= 6-30 minutes

    1=31-60 minutes

    0= More than 60 min

2. Do you find it difficult to refrain from smoking in places where it is forbidden, (e.g. in church, at the library, in the cinema)?

    0 = No

    1 = Yes

3. Which cigarette would hate most to give up?

    1 = The first one in the morning

    0 = All others

4. How many cigarettes per day do you smoke?

    0= 10 or less

    1= 11-20

    2= 21-30

    3= 31 or more

5. Do you smoke more frequently during the first hours after waking than the rest of the day?

    0 = No

    1 = Yes

6. Do you smoke when you are so ill that you are in bed most of the day?

    0 = No

    1 = Yes

Calculate: Add scores of all 6 items.

1-2 = low dependence

3-4 = low-moderate dependence

5-7 = moderate dependence

8+ = high dependence

APPENDIX 7: Recent Smoking Questionnaire

The follow questions are about your recent smoking

1. In the last 30 days, have you smoked at all - even a puff?

1=YES

2 =NO

0 = Don't know

2. In the last 7 days, have you smoked at all - even a puff?

1=YES

2 = No

0 = Don't know

3. In the last 7 days, how many days did you smoke cigarettes?

____ [0-7]

4. In the last 7 days, how many cigarettes have you smoked per **day?**

_____ [0-99]

APPENDIX 8: Screening Week Diary

Date	Record the number of cigarettes that you smoked each day.	Baseline Visit *Office Use Only*
____/____ D1	_____ # of cigs	○
____/____ D2	_____ # of cigs	○
____/____ D3	_____ # of cigs	○
____/____ D4	_____ # of cigs	○
____/____ D5	_____ # of cigs	○
____/____ D6	_____ # of cigs	○
____/____ D7	_____ # of cigs	○

Date	Record the number of cigarettes that you smoked each day.	Baseline Visit *Office Use Only*
____/____ D8	_____ # of cigs	○
____/____ D9	_____ # of cigs	○
____/____ D10	_____ # of cigs	○
____/____ D11	_____ # of cigs	○
____/____ D12	_____ # of cigs	○
____/____ D13	_____ # of cigs	○
____/____ D14	_____ # of cigs	○

APPENDIX 9: Smoking, Medication Use, Urges and Mood & Diary

Duke Center for Smoking Cessation
Study Name: Axsome
Principal Investigator: James Davis, MD

Subject Number: AX_____
Subject Initials: _____
Date: _____

Visit 1 to 2: Smoking, Medication Use, Urges, and Mood & Diary

Urges: On a scale from 1 to 10, how strong have your urges to smoke been today with 1 being not at all bad, and 10 being extremely bad?
Mood: One a scale from 1 to 10, how bad have your moods been today with 1 being not at all bad, and 10 being extremely bad?

	Date	# Cigarettes Smoked	Medication Use	How many Urges to Smoke did you experience today?	Urge Strength (scale 1-10)	Mood (scale 1-10)
1 Visit 1 Date	____/____	_____				
2	____/____	_____	START MEDICATION Bottle # _____ O Morning Dose			
3	____/____	_____	O Morning Dose			
4	____/____	_____	O Morning Dose			
5	____/____	_____	O Morning Dose O Evening Dose			
6	____/____	_____	O Morning Dose O Evening Dose			
7	____/____	_____	O Morning Dose O Evening Dose			
DATE/TIME OF VISIT 2						

Did you take your morning dose **before** coming in for Visit 2? O Yes O No | ***Office use only:*** (Bottle #: _____)

Did you take your evening dose **before** coming in for Visit 2? O Yes O No | ***Office use only:*** (Bottle #: _____)

Duke Center for Smoking Cessation
Study Name: Axsome
Principal Investigator: James Davis, MD

Subject Number: AX_____
Subject Initials: _____
Date: _____

Visit 2 to 3: Smoking, Medication Use, Urges, and Mood & Diary

Urges: On a scale from 1 to 10, how strong have your urges to smoke been today with 1 being not at all bad, and 10 being extremely bad?
Mood: One a scale from 1 to 10, how bad have your moods been today with 1 being not at all bad, and 10 being extremely bad?

	Date	# Cigarettes Smoked	Medication Use	How many Urges to Smoke did you experience today?	Urge Strength (scale 1-10)	Mood (scale 1-10)
1 Visit 3 Date	____/____	_____	O Morning Dose (Bottle # _____) O Evening Dose (Bottle # _____)			
2	____/____	_____	O Morning Dose O Evening Dose			
3	____/____	_____	O Morning Dose O Evening Dose			
4	____/____	_____	O Morning Dose O Evening Dose			
5	____/____	_____	O Morning Dose O Evening Dose			
6	____/____	_____	O Morning Dose O Evening Dose			
7	____/____	_____	O Morning Dose O Evening Dose			
DATE/TIME OF VISIT 3						

Did you take your morning dose **before** coming in for Visit 3? O Yes O No | ***Office use only:*** (Bottle #: _____)

Did you take your evening dose **before** coming in for Visit 3? O Yes O No | ***Office use only:*** (Bottle #: _____)

Duke Center for Smoking Cessation
Study Name: Axsome
Principal Investigator: James Davis, MD

Subject Number: AX_____
Subject Initials: _____
Date: _____

Visit 3 to 4: Smoking, Medication Use, Urges, and Mood & Diary

Urges: On a scale from 1 to 10, how strong have your urges to smoke been today with 1 being not at all bad, and 10 being extremely bad?
Mood: One a scale from 1 to 10, how bad have your moods been today with 1 being not at all bad, and 10 being extremely bad?

	Date	# Cigarettes Smoked	Medication Use	How many Urges to Smoke did you experience today?	Urge Strength (scale 1-10)	Mood (scale 1-10)
1 Visit 3 Date	____/____	_____	O Morning Dose (Bottle # _____) O Evening Dose (Bottle # _____)			
2	____/____	_____	O Morning Dose O Evening Dose			
3	____/____	_____	O Morning Dose O Evening Dose			
4	____/____	_____	O Morning Dose O Evening Dose			
5	____/____	_____	O Morning Dose O Evening Dose			
6	____/____	_____	O Morning Dose O Evening Dose			
7	____/____	_____	O Morning Dose O Evening Dose			
DATE/TIME OF VISIT 4		Did you take your morning dose **before** coming in for Visit 4? O Yes O No | ***Office use only:*** (Bottle #: _____) Did you take your evening dose **before** coming in for Visit 4? O Yes O No | ***Office use only:*** (Bottle #: _____)				

Duke Center for Smoking Cessation
Study Name: Axsome
Principal Investigator: James Davis, MD

Subject Number: AX_____
Subject Initials: _____
Date: _____

Visit 4 to 5: Smoking, Medication Use, Urges, and Mood & Diary

Urges: On a scale from 1 to 10, how strong have your urges to smoke been today with 1 being not at all bad, and 10 being extremely bad?
Mood: One a scale from 1 to 10, how bad have your moods been today with 1 being not at all bad, and 10 being extremely bad?

	Date	# Cigarettes Smoked	Medication Use	How many Urges to Smoke did you experience today?	Urge Strength (scale 1-10)	Mood (scale 1-10)
1 Visit 4 Date	____/____	_____	O Morning Dose (Bottle # _____) O Evening Dose (Bottle # _____)			
2	____/____	_____	O Morning Dose O Evening Dose			
3	____/____	_____	O Morning Dose O Evening Dose			
4	____/____	_____	O Morning Dose O Evening Dose			
5	____/____	_____	O Morning Dose O Evening Dose			
6	____/____	_____	O Morning Dose O Evening Dose			
7	____/____	_____	O Morning Dose O Evening Dose			
DATE/TIME OF VISIT 5						

Did you take your morning dose **before** coming in for Visit 5? O Yes O No | ***Office use only:*** (Bottle #: _____)
Did you take your evening dose **before** coming in for Visit 5? O Yes O No | ***Office use only:*** (Bottle #: _____)

Subject Number: AX______________

Subject Initials: ______________

Continuation from Diary for Visit _______ to Visit ________

In the event of a missed/rescheduled/cancelled appointment – *please continue to complete daily diary enters until your next appointment*:

Urges: On a scale from 1 to 10, how strong have your urges to smoke been today with 1 being not at all bad, and 10 being extremely bad?

Mood: One a scale from 1 to 10, how bad have your moods been today with 1 being not at all bad, and 10 being extremely bad?

Day #	Date	# Cigarettes Smoked	Medication Use	How many Urges to Smoke did you experience today?	Urge Strength (scale 1-10)	Mood (scale 1-10)	Visit #
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5
	___/___	_____	O Morning Dose (Bottle # _______) O Evening Dose (Bottle # _______)				O V2 O V3 O V4 O V5

Did you take your morning dose **before** coming in for Visit ____? O Yes O No | ***Office use only:*** (Bottle #: __________)

Did you take your evening dose **before** coming in for Visit _____? O Yes O No | ***Office use only:*** (Bottle #: __________)

APPENDIX 10: Medication Side Effects Questionnaire

Duke Center for Smoking Cessation
Study Name: Impact of AXS-05 on Smoking
Principal Investigator: James M. Davis M.D.

Subject Number: AX_____
Subject Initials: _____
Date: _____
Visit # ☐

Medication Side Effects Questionnaire

Have you experienced any side effects from the study drug you are taking? ○ **Yes** ○ **No**

If yes, please fill out the information below.

Side Effect 1:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 2:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 3:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 4:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			

IF YOU REPORTED SIDE EFFECTS ABOVE:

Did you stop the study medication as a result of the side effect(s) you listed above? O YES O NO

APPENDIX 11: Mood and Physical Symptoms Scale-2[68]

The next questions are about how you have been feeling over the past 24 hours.

1. How much of the time have you felt the urge to smoke in the past 24 hours?

   0=Not at all

   1=A little of the time

   2=A lot of the time

   3=Almost all of the time

   4= All of the time

2. How strong have the urges been?

   0=No urge

   1=Slight

   2=Moderate

   3=Strong

   4=Very Strong

   5=Extremely Strong

Calculate: Please add scores of questions above
0-2 = Mild
3-6 = Moderate
7-10 = Severe

APPENDIX 12: State-Trait Anxiety Inventory[70]

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right now*, that is *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately So	Very Much So
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally feel*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe you generally feel.

	Almost Never	Sometimes	Often	Almost Always
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that doesn't really matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Scoring: The total score ranges from 0–63. The following guidelines are recommended for the interpretation of scores: 0–9, normal or no anxiety; 10–18, mild to moderate anxiety; 19–29, moderate to severe anxiety; and 30–63, severe anxiety.

APPENDIX 13: Center for Epidemiologic Studies Depression Scale-R

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week

	Not at all *or Less than 1 day*	1-2 days	3-4 days	5-7 days	Nearly every day for 2 weeks
1. My appetite was poor					
2. I could not shake off the blues.					
3. I had trouble keeping my mind on what I was doing.					
4. I felt depressed					
5. My sleep was restless					

6. I felt sad					
7.I could not get going					
8. Nothing made me happy					
9. I felt like a bad person					
10. I lost interest in my usual activities					
11. I slept much more than usual					
12. I felt like I was moving too slowly					
13. I felt fidgety					
14. I wished I were dead					
15. I wanted to hurt myself					
16. I was tired all the time					
17. I did not like myself					
18. I lost a lot of weight without trying to					
19. I had a lot of trouble getting to sleep					
20. I could not focus on the important things.					

APPENDIX 14: Minnesota Nicotine Withdrawal Scale (MNWS)[69]

Behavior Rating Scale

Self-Report

Please rate yourself for the period for the last 24 hours.

DSM – 5 Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
1. Angry, irritable, frustrated	0	1	2	3	4
2. Anxious, nervous	0	1	2	3	4
3. Depressed mood, sad	0	1	2	3	4
4. Difficulty concentrating	0	1	2	3	4
5. Increased appetite, hungry, weight gain	0	1	2	3	4
6. Insomnia, sleep problems, awakening at night	0	1	2	3	4
7. Restlessness	0	1	2	3	4
Other Validated Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
8. Desire or craving to smoke	0	1	2	3	4
Other Possible Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
9. Constipation	0	1	2	3	4
10. Coughing	0	1	2	3	4
11. Decreased pleasure from events	0	1	2	3	4
12. Dizziness	0	1	2	3	4
13. Drowsy	0	1	2	3	4
14. Impatient	0	1	2	3	4
15. Impulsive	0	1	2	3	4

TOTAL Score Questions 1-15: ____

APPENDIX 15: Pittsburgh Sleep Quality Index (PSQI)[77]

The following questions relate to your usual sleep habits during the past week only. Your answers should indicate the most accurate reply for the majority of days and nights in the past week. Please answer all questions.

1. During the past week, what time have you usually gone to bed at night? _____ Bed time
2. During the past week, how long (in minutes) has it usually taken you to fall asleep each night? _____ Number of minutes
3. During the past week, what time have you usually gotten up in the morning? _____ Getting up time
4. During the past week, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____ Hours of sleep per night

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past week, how often have you had trouble sleeping because you…

	Not during the past week	Once in the past week	Twice in the last week	Three or more times in the last week
a. Cannot get to sleep within 30 minutes	0	1	2	3
b. Wake up in the middle of the night or early morning	0	1	2	3
c. Have to get up to use the bathroom	0	1	2	3
d. Cannot breathe comfortably	0	1	2	3
e. Cough or snore loudly	0	1	2	3
f. Feel too cold	0	1	2	3
g. Feel too hot	0	1	2	3
h. Had bad dreams	0	1	2	3
i. Have pain	0	1	2	3
j. Other reasons (please describe)	0	1	2	3

	Not during the past week	Once in the past week	Twice in the last week	Three or more times in the last week
6. During the past week, how often have you taken medicine to help you sleep (prescribed or over-the counter)?	0	1	2	3
7. During the past week, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	0	1	2	3

8. During the past week, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

a. 0 - No problem at all
b. 1 - Only a very slight problem
c. 2 - Somewhat of a problem
d. 3 - A very big problem

9. During the past week, how would you rate your sleep quality overall?

a. 0 - Very good

b. 1 - Fairly good

c. 2 - Fairly bad

d. 3 - Very bad

10. Do you have a bed partner or roommate?

a. 0 - No bed partner or roommate
b. 1 - Partner/roommate in other room
c. 2 - Partner in same room, but not same bed
d. 3 - Partner in same bed

If you have a roommate or bed partner, ask him/her how often in the past week you have had…

	Not during the past week	Once in the past week	Twice in the last week	Three or more times in the last week
a. Loud snoring	0	1	2	3
b. Long pauses between breaths while asleep	0	1	2	3
c. Legs twitching or jerking while you sleep	0	1	2	3
d. Episodes of disorientation or confusion during sleep	0	1	2	3
e. Other restlessness while you sleep (please describe)	0	1	2	3

Scoring PSQI

Component Number	Criteria	Values	Total Score Scale	Component Score
Component 1	Q9	**(Q9):** _____	**N/A**	___
Component 2	Q2 + Q5a ***Question 2 Scale:*** **Time Score** **≤15 min 0** **16-30 min 1** **31-60 min 2** **>60 min 3**	**(Q2):** _____ + **(Q5a):** _____ = _____	**Sum Score** **0 0** **1-2 1** **3-4 2** **5-6 3**	___
Component 3	Q4	**(Q4):** _____	**N/A**	___
Component 4	#hours slept X 100% #hours in bed ***Look at Q1,3, and 4 for these values***	**#hours slept:** ____ X **100%** = _____ **#hours in bed:**	**% Score** **>85% 0** **75-85% 1** **65-75% 2** **<65% 3**	___
Component 5	Sum of Q5b through Q5j	**(Q5b):** _____ **(Q5c):** _____ **(Q5d):** _____ **(Q5e):** _____ **(Q5f):** _____ **(Q5g):** _____ **(Q5h):** _____ **(Q5i):** _____ + **(Q5j):** _____ = _____	**Sum Score** **0 0** **1-9 1** **10-18 2** **19-27 3**	___

Component 6	Q6	**(Q6): _____**	**N/A**	___
Component 7	Q7 + Q8	**(Q7): _____ + (Q8): _____ = _____**	**Sum Score** **0 0** **1-2 1** **3-4 2** **5-6 3**	___

Total Score (Sum of Components 1-7): ___

APPENDIX 16: Brief Agitation Measure[90]

Instructions: Please read each item below and indicate to what extent you feel the statement describes you.

Rate each statement on the scale below:

	Strongly Disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly Agree
1)Recently, I want to crawl out of my skin	0	1	2	3	4	5	6
2) Recently, I feel so stirred up inside I want to scream	0	1	2	3	4	5	6
3) Recently, I feel a lot of emotional turmoil in my gut	0	1	2	3	4	5	6

APPENDIX 17: End of Treatment Follow-Up - Side Effects Questionnaire

Have you experienced any side effects following the end of treatment over the last two weeks? ○ Yes ○No

If yes, could you please describe the side effect you are experiencing, its frequency and severity:

Duke Center for Smoking Cessation
Study Name: Impact of AXS-05 on Smoking
Principal Investigator: James M. Davis M.D.

Subject Number: AX_____
Subject Initials: _____
Date: _____
Visit # ☐

End of Treatment - Side Effects Questionnaire

Have you experienced any side effects from the study drug you are taking? ○ **Yes** ○**No**

If yes, please fill out the information below.

Side Effect 1:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 2:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 3:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 4:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			

APPENDIX 18: SCOFF Questionnaire (Eating Disorder Screen)[18]

S – Do you make yourself **S**ick because you feel uncomfortably full?

○ Yes ○ No

C – Do you worry you have lost **C**ontrol over how much you eat?

○ Yes ○ No

O – Have you recently lost more than 14 pounds (lbs) in a three-month period?

○ Yes ○ No

F – Do you believe yourself to be **F**at when others say you are too thin?

○ Yes ○ No

F – Would you say **F**ood dominates your life?

○ Yes ○ No

An answer of 'yes' to two or more questions warrants further questioning and more comprehensive assessment

A further two questions have been shown to indicate a high sensitivity and specificity for bulimia nervosa. These questions indicate a need for further questioning and discussion.

1. Are you satisfied with your eating patterns?
   ○ Yes ○ No

2. Do you ever eat in secret?

   ○ Yes ○ No

APPENDIX 19: Mood Disorder Questionnaire (MDQ)[91]

Has there ever been a period of time when you were not your usual self and…	Yes	No
... you felt so good or so hyper that other people thought you were not your normal self, or you were so hyper that you got into trouble?		
... you were so irritable that you shouted at people or started fights or arguments?		
... you felt much more self-confident than usual?		
... you got much less sleep than usual and found you didn't really miss it?		
... you were much more talkative or spoke much faster than usual?		
... thoughts raced through your head or you couldn't slow your mind down?		
... you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
... you had much more energy than usual?		
... you were much more active or did many more things than usual?		
... you were much more social or outgoing than usual; for example, you telephoned friends in the middle of the night?		
... you were much more interested in sex than usual?		
... you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
... spending money got you or your family into trouble?		
If you checked YES to more than one of the above, have several of these ever happened during the same period of time?		
How much of a problem did any of these cause you- like being unable to work; having family, money, or legal troubles, getting into arguments or fights?		

No Problems	Minor Problems	Moderate Problems	Serious Problems

APPENDIX 20: Modified Mini Screen (MMS) (Psychotic Disorders)[17]

Please select "Yes" or "No" for each question	**Yes**	No
Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you?		
Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?		
Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Or, have you ever felt that you were possessed?		
Have you ever believed that you were being sent special messages through the TV, radio, or newspaper? Did you believe that someone you did not personally know was particularly interested in you?		
Have your relatives or friends ever considered any of your beliefs strange or unusual?		
Have you ever heard things other people couldn't hear, such as voices?		
Have you ever had visions when you were awake or have you ever seen things other people couldn't see?		

APPENDIX 21: Columbia Suicide Severity Rating Scale (C-SSRS)[92]

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 1 month**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*) Recent - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 3 months
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted _____	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐ Total # of preparatory acts _____	Yes ☐ No ☐ Total # of preparatory acts _____

	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX 22: Brief Psychiatric Rating Scale (BPRS)[93]

CLIENT NAME: _____ DATE: _____
CLIENT ID#: _____ MD: _____

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. **SOMATIC CONCERN** Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	SCORE	10. **HOSTILITY** Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (*Rate attitude toward interviewer under "uncooperativeness"*).	SCORE
2. **ANXIETY** Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	SCORE	11. **SUSPICIOUSNESS** Brief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.	SCORE
3. **EMOTIONAL WITHDRAWAL** Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	SCORE	12. **HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	SCORE
4. **CONCEPTUAL DISORGANIZATION** Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	SCORE	13. **MOTOR RETARDATION** Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.	SCORE
5. **GUILT FEELINGS** Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	SCORE	14. **UNCOOPERATIVENESS** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	SCORE
6. **TENSION** Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	SCORE	15. **UNUSUAL THOUGHT CONTENT** Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.	SCORE
7. **MANNERISMS AND POSTURING** Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	SCORE	16. **BLUNTED AFFECT** Reduced emotional tone, apparent lack of normal feeling or involvement.	SCORE
8. **GRANDIOSITY** Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	SCORE	17. **EXCITEMENT** Heightened emotional tone, agitation, increased reactivity.	SCORE
9. **DEPRESSIVE MOOD** Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.	SCORE	18. **DISORIENTATION** Confusion or lack of proper association for person, place or time.	SCORE

The Study Clinician (MD/PA) will conduct an interview with the participant that addresses the 18 symptom constructs found below. Each construct will be assessed on a scale of 0 to 7, zero indicating "not assessed" and 7 indicating "extremely severe" symptoms.

APPENDIX 23: Perceived Stress Scale (PSS-4)[94]

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you felt that you were unable to control the important things in your life?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

2. In the last month, how often have you felt confident about your ability to handle your personal problems?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

3. In the last month, how often have you felt that things were going your way?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

APPENDIX 24: Modified Cigarette Evaluation Questionnaire (mCEQ)[95]

If you have smoked since you last completed this questionnaire, please mark the number that best represents how smoking made you feel.

(1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

1. Was smoking satisfying? _____

2. Did cigarettes taste good? _____

3. Did you enjoy the sensations in your throat and chest? _____

4. Did smoking calm you down? _____

5. Did smoking make you feel more awake? _____

6. Did smoking make you feel less irritable? _____

7. Did smoking help you concentrate? _____

8. Did smoking reduce your hunger for food? _____

9. Did smoking make you dizzy? _____

10. Did smoking make you nauseous? _____

11. Did smoking immediately relieve your craving for a cigarette? _____

12. Did you enjoy smoking? _____

APPENDIX 25: Demographics Form

Basic Demographics

Age _____ Date of Birth _____

Gender: ○ Male ○ Female ○ Transgender Female ○Transgender Male ○Prefer not to answer

Race

○ White
○ Black or African American
○ Asian
○ Native Hawaiian or Other Pacific Islander
○ American Indian or Alaska Native
○ Other
○ More than one race

Ethnic Category ○ Hispanic or Latino ○ Not Hispanic or Latino

What is the highest level of schooling you have completed?

○ Elementary school or less
○ Some high school
○ High school graduate or equivalent
○ Some college or technical/vocational school
○ College graduate or higher

APPENDIX 26: Contact information Form

Contact Information Form

Please fill in the following information about yourself:

First Name _____ M.I. _____ Last Name _____

Number and Street Address _____

City_____ State _____ Zip code _____

Email address _____

Primary Telephone # _____ Other Telephone # _____

Do you give CSC permission to leave a message at the above numbers or contact you by email?

- ○ Yes
- ○ No

If I cannot be reached or if there is an emergency, you can leave a message with:

Name _____ Telephone # _____

I understand in the event that I do not return messages and fail to come to appointments my emergency contact person may be contacted.

Participant's Signature _____ Date _____

APPENDIX 27: Review of Systems (ROS)

Review of Systems – Page 1

Are you currently (in the last 30 days) being treated for any of the following conditions?

General:
- ○ None of these apply
- ○ Unexplained weight loss or gain
- ○ Fever or chills
- ○ Fatigue / lack of energy
- ○ Weakness
- ○ Trouble sleeping

Skin:
- ○ None of these apply
- ○ Rashes
- ○ Lumps
- ○ Color change
- ○ Hair and nail changes

Head:
- ○ None of these apply
- ○ Headache
- ○ Head injury

Ears:
- ○ None of these apply
- ○ Decreased hearing
- ○ Earache
- ○ Ringing in the ears

Eyes:
- ○ None of these apply
- ○ Vision problems
- ○ Specks
- ○ Blurry or double vision
- ○ Flashing lights
- ○ Redness
- ○ Pain

Nose:
- ○ None of these apply
- ○ Stuffiness
- ○ Discharge
- ○ Itching
- ○ Sinus pain
- ○ Nose bleeds

Throat:
- ○ None of these apply
- ○ Teeth/gum problems
- ○ Dentures
- ○ Hoarseness
- ○ Sore tongue
- ○ Dry mouth
- ○ Sore throat
- ○ Thrush
- ○ Non-healing sores
- ○ Difficulty swallowing

Neck:
- ○ None of these apply
- ○ Lumps
- ○ Stiffness
- ○ Pain
- ○ Swollen glands

Respiratory:
- ○ None of these apply
- ○ Cough (dry or wet, productive)
- ○ Shortness of breath
- ○ Coughing up blood
- ○ Painful breathing
- ○ Wheezing

Cardiovascular:
- ○ None of these apply
- ○ Chest pain or discomfort
- ○ Tightness
- ○ Heart pounding/fluttering/ palpitations
- ○ Difficulty breathing lying down
- ○ Swelling
- ○ Shortness of breath with activity
- ○ Suddenly awaking from sleep with shortness of breath

Gastrointestinal:
- ○ None of these apply
- ○ Swallowing difficulties
- ○ Heartburn
- ○ Constipation
- ○ Vomiting
- ○ Change in bowel habits
- ○ Rectal bleeding
- ○ Diarrhea
- ○ Stomach pain
- ○ Yellow eyes or skin
- ○ Change in appetite
- ○ Nausea

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Urinary:
- ○ None of these apply
- ○ Frequency
- ○ Urgency
- ○ Blood in urine
- ○ Pain with urination
- ○ Change in urinary strength
- ○ Incontinence

Vascular:
- ○ None of these apply
- ○ Calf pain with walking
- ○ Leg cramping
- ○ Leg pains

Musculoskeletal:
- ○ None of these apply
- ○ Muscle or joint pain
- ○ Stiffness
- ○ Back pain
- ○ Swelling of joints
- ○ Trauma

Neurologic:
- ○ None of these apply
- ○ Dizziness
- ○ Fainting
- ○ Tingling
- ○ Weakness
- ○ Numbness
- ○ Tremor
- ○ Shaking episodes

Hematologic:
- ○ None of these apply
- ○ Bruise easily
- ○ Bleed easily

Endocrine:
- ○ None of these apply
- ○ Heat or cold intolerance
- ○ Sweating
- ○ Frequent urination
- ○ Thirst
- ○ Change in appetite

Psychiatric:
- ○ None of these apply
- ○ Nervousness
- ○ Memory loss
- ○ Feeling down

Females only
- ○ None of these apply
- ○ Pregnant or currently breast feeding

PA / MD Signature _____ Date _____

APPENDIX 28: Alcohol Use Disorders Identification Test (Audit-C)

1. How often do you have a drink containing alcohol?
    (0) Never
    (1) Monthly or less
    (2) 2 to 4 times a month
    (3) 2 to 3 times a week
    (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
    (0) 1 or 2
    (1) 3 or 4
    (2) 5 or 6
    (3) 7, 8, or 9
    (4) 10 or more

3. How often do you have six or more drinks on one occasion?
    (0) Never
    (1) Less than monthly
    (2) Monthly
    (3) Weekly
    (4) Daily or almost daily

TOTAL**_____** 4 or greater for men is considered a positive screen; 3 or greater for women is considered a positive screen.

APPENDIX 29: 6 Week Follow-Up Smoking Status Questions

Finally, I have two additional questions I would like to ask you about your recent smoking history.

1. In the last 7 days, have you smoked at all – even a puff? O Yes O No
2. In the last 7 days, how many cigarettes, on average, have you smoked per day? _____

If the participant answers "NO" to question 1 and zero cigarettes to question 2, ask the participant when they smoked their last cigarette:

When was the date of your last cigarette? _____