Protocol ACH-CYT-10 (ORCA-V1 Trial)

A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adults Using Nicotine-containing E-cigarettes

May 4, 2022

Version 3.0

CONFIDENTIAL

SYNOPSIS

Protocol Number: ACH-CYT-10 (ORCA-V1 Trial)
Sponsor: Achieve Life Sciences, Inc
Title of Study: A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adults Using Nicotine-containing E-cigarettes
Clinical Phase: Phase 2
Study Population: Male and female subjects ≥18 years who vape nicotine e-cigarettes daily and intend to make a quit attempt during the study.
Rationale: (-)-Cytisine is a naturally occurring plant-based alkaloid, isolated from seeds of *Cytisus laburnum* (Golden chain acacia), and acts as a partial antagonist with high affinity and specificity for neuronal nicotinic ($\alpha_4\beta_2$) receptors. Cytisine can reduce the severity of nicotine withdrawal symptoms as well as inhibiting nicotine reward effects by targeting nicotinic acetylcholine receptors (nAChRs) in the brain. Cytisine has been used as a smoking cessation drug since the 1960's in Central and Eastern European countries, where initial clinical studies were conducted. Previous studies dating from decades ago and more recently two Phase 3 studies (published in 2011 and 2014) have shown that cytisine can be more effective than placebo as well as nicotine replacement therapy (NRT) in helping people to stop smoking. In 2018, the United States Adopted Names (USAN) Council adopted "cytisinicline" as the nonproprietary, or generic, name for cytisine. One increasingly popular alternative to smoking cigarettes is the use of electronic cigarettes (e-cigarettes), or vaping, which delivers liquid nicotine into a mist or aerosol which is inhaled. This method of consumption avoids or lowers exposure to many of the toxic chemicals associated with cigarette smoke but may have other associated health and safety issues. The emerging use of e-cigarettes is resulting in a population of people addicted to a new source of nicotine. According to the Annals of Internal Medicine, data reported in 2018 estimated that approximately 10.8 million American adults use e-cigarettes and half of these users are age 18-34 years.[1] The United States Food and Drug Administration, or FDA, considers e-cigarette use an epidemic, particularly in youth, and the National Institute on Drug Abuse, or NIDA, a division of the NIH, has tobacco/nicotine and vaping on their list of Drugs of Abuse. Not only does e-cigarette use come with risks of its own, but research has also shown that young adults who vape are more likely to start smoking combustible cigarettes later in life. This is an important area of focus given the increasing number of vaping-related lung illnesses that have recently been reported. The number of e-cigarette users continues to grow and while e-cigarettes have been viewed as safer than combustible cigarettes, the long-term safety of e-cigarettes is still unproven and may sustain nicotine addiction.

Prior trials already have demonstrated cytisinicline's efficacy in helping people quit smoking. This clinical study will evaluate the potential benefit of cytisinicline in treating nicotine addiction among users whose only source of nicotine is via the use of e-cigarettes. Given the mechanism of action of cytisinicline, this study will assess whether cytisinicline given to users of nicotine-containing e-cigarettes but not combustible tobacco products (i.e., conventional cigarettes) can reduce nicotine dependence and promote vaping cessation or reduction. As an added value, this study will evaluate the same safety parameters as the Phase 3 studies for cigarette smoking cessation and hence will add to the growing safety database for cytisinicline.

In this study, all references to vaping means the use of nicotine-containing e-cigarettes or other nicotine-containing vaping devices. Subjects will be randomized 2:1 to receive either 3 mg cytisinicline TID for 12 weeks plus standard behavioral support (Arm B: cytisinicline TID) or placebo TID for 12 weeks plus standard behavioral support (Arm A: placebo TID). The primary outcome assessment will be nicotine vaping cessation during Weeks 9-12. Vaping cessation is defined as weekly nicotine vaping abstinence for 4 consecutive weeks. Other timing for weekly vaping abstinence/cessation (e.g., Weeks 3-6 or Weeks 6-9) and any reduction in nicotine vaping will be analyzed as secondary outcomes.

This study will also assess the safety profile of 3 mg cytisinicline administered TID for 12 weeks.

Objectives:

Primary Efficacy Objective:

Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of nicotine vaping cessation from Week 9 to Week 12 post-randomization as compared to subjects randomized to Arm A (placebo TID for 12 weeks plus behavioral support).

Secondary Efficacy Objectives:

1) Assess whether subjects randomized to Arm B (cytisinicline TID) can achieve vaping abstinence/cessation at any time during treatment or reduce their daily vaping as objectively measured with biomarkers of nicotine exposure compared to subjects randomized to Arm A (placebo TID). Specific Secondary Efficacy Objectives related to this are described below:
    - Assess whether subjects randomized to Arm B have a higher probability of achieving vaping cessation between Week 3 and Week 9 post-randomization (e.g., Week 3-6 or Week 6-9,) as compared to subjects randomized to Arm A.
    - To compare arms (Arm A vs Arm B) on 7-day point prevalence rates for vaping abstinence on a weekly basis from Week 2 to Week 12.
    - To compare arms (Arm A vs Arm B) for a reduction in nicotine vaping using weekly quantitative cotinine levels from Week 2 to Week 12.
2) Assess whether subjects randomized to Arm B have a higher probability for continuous vaping abstinence between Week 9 and Week 16 post-randomization

(i.e., subjects achieving primary endpoint abstinence with continued abstinence through follow-up).

Other Objectives:

Explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.

Evaluate for nicotine withdrawal symptoms at Weeks 1-4 and again for any possible withdrawal symptoms due to study drug discontinuation pre- and post-Week 12.

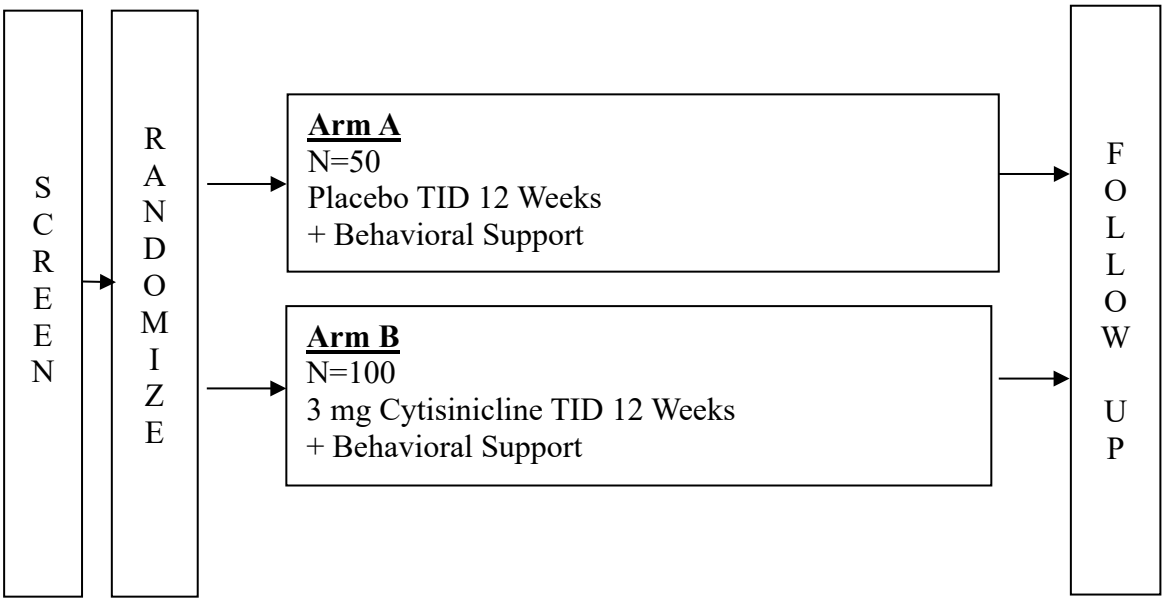
Safety Objectives:

To evaluate the safety profile of 3 mg TID cytisinicline when administered for 12 weeks.

Study Design:

This will be a multi-center, double-blind, randomized, placebo-controlled, Phase 2 study conducted in male or female adults who are daily nicotine e-cigarette users only (i.e., vaping only subjects as confirmed with a positive salivary cotinine sample and a carbon monoxide [CO] breath sample <10 ppm), intending to try to quit vaping, and willing to set a quit date that is within 7-14 days from the start of cytisinicline treatment. Study treatment must start the day after randomization.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. A total of approximately 150 subjects will be randomly assigned (2:1) to one of two Arms: (Arm B, 12 weeks cytisinicline + behavior support: N=100 or Arm A, 12 weeks of placebo+ behavior support: N=50) as shown in the study design figure below.



Vaping quit status (abstinence) will be assessed starting at Week 2 (Day 14±1) and assessments will continue weekly during the Treatment Period through to Week 12 and at Week 16 in the follow up period. In addition, assessments for cotinine in saliva and expired CO levels will be performed during the treatment period and will be compared to baseline

measures. All subjects will receive concurrent nicotine cessation behavioral support during the study Treatment Period (Week 1-12).

Safety assessments at clinic visits will occur weekly throughout the Treatment Period. Laboratory hematology and chemistry assessments will be made on Day 7, Week 6 and Week 12 during the Treatment Period. Adverse events will be monitored through the follow up period. Any ongoing adverse events at Week 16 will be followed until resolved or determined to be chronic. The end of study is defined as the last follow up visit (Week 16) for the last subject.

Selection Criteria

Inclusion Criteria:

1. Male or female subjects, age ≥18 years.
2. Test positive for cotinine using the Alere iScreen® OFD Cotinine Oral Fluid Screening Device (Positive testing at ≥30 ng/mL cotinine level).
3. Current daily nicotine-containing electronic cigarette usage as recorded in a screening diary for at least 7 consecutive days. Willing to bring the e-cigarette or nicotine device used to the clinical site so that the specific product type, flavor, and nicotine level can be documented.
4. Willing to initiate study treatment on the day after randomization and set a quit date within 7-14 days of starting treatment.
5. Willing to actively participate in the study's vaping cessation behavioral support provided throughout the study.
6. Able to fully understand study requirements, willing to participate, and comply with dosing schedule.
7. Sign the Informed Consent Form.

Exclusion Criteria:

1. Currently smoking, or having smoked within 4 weeks prior to study randomization, any combustible cigarettes, other combustible tobacco products or non-combustible tobacco products (such as heat not burn products) (i.e., dual users).
2. Expired Carbon Monoxide (CO) levels ≥10 ppm, indicating recent combustible tobacco use.
3. More than 1 study participant in same household during the study treatment period.
4. Known hypersensitivity to cytisinicline or any of the excipients.
5. Positive urinary drugs of abuse screen determined within 28 days before the first dose of cytisinicline (Note: THC is not part of the abuse screen).
6. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (i.e., requiring treatment or monitoring).
7. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (i.e., requiring treatment or further assessment).

8. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
9. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).
10. Documented diagnosis of schizophrenia or bipolar psychiatric illness; currently psychotic; having suicidal ideation within the last 3 months (corresponding to question 4 or 5 on the C-SSRS); or current symptoms of moderate to severe depression (depression score ≥11 on the HADS) within the last 3 months.
11. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation).
12. Hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
13. Recent history or symptoms (within 4 weeks of randomization) of unstable respiratory disease (e.g., pneumonia, product-use associated lung injury or EVALI, etc.)
14. Women who are pregnant or breast-feeding.
15. Male or female subjects of childbearing potential who do not agree to use acceptable methods of birth control starting at the time of consent, during the study treatment period, and continuing for one month after ending study treatment.
16. Participation in a clinical study with an investigational drug in the 4 weeks prior to study randomization.
17. Use of other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) in the 4 weeks prior to study randomization, any previous cytisine use or planned use of these or other nicotine replacement medications during the study.
18. Any planned use during the study of combustible cigarettes or other nicotine-containing, non-vaping products (e.g., pipe tobacco, cigars, snuff, smokeless tobacco, hookah, ZYN pouches, etc).
19. Any other reason that the investigator views the subject should not participate or would be unable to fulfill the requirements for the study.

Number of Subjects, Randomization, and Stratification:

Approximately 150 subjects will be randomized (2:1) at 5-8 sites in the United States, with 100 subjects in the cytisinicline arm and 50 subjects in the placebo arm. Subjects will be stratified on whether they have smoked >100 cigarettes in their lifetime (yes vs no).

Study Treatments:

Identical appearing tablets containing 3 mg cytisinicline or matched placebo will be administered orally. During the 12-week Treatment Period, subjects will take one tablet three times daily. Tablets will be blister sealed and configured into medication packs for one week of dosing. Each pack will contain 21 tablets for TID dosing for 7 days. Six weeks of dosing packs will be contained in a carton such that 2 cartons will be assigned to a subject during the study treatment (i.e., 12 total packs for 12 weeks of study treatment).

Clinic staff will distribute and collect packs as the subject progresses through the clinic visits and will conduct ongoing accountability during each weekly clinic visit by reviewing a subject's treatment diary and associated blister packs. Used packs will be retained so that the Sponsor's monitoring staff can verify accountability records.

Duration of Study:

All randomized subjects will initiate study treatment the day after randomization and receive 12 weeks of treatment. Duration of this study is estimated to be approximately 16 weeks for an individual subject (from randomization to Week 16 follow up visit).

Study Procedures:

Prior to taking part in the trial, subjects will be provided with an informed consent document outlining study requirements and procedures. Subjects will be given adequate time to review, discuss, and decide whether they wish to participate.

Subjects providing signed informed consent will be assessed during the Screening Period to determine their eligibility for the trial and to complete their daily e-cigarette or device usage in the screening diary. Subjects must complete 7 consecutive days in the screening diary for confirmation of eligibility. If eligible, subjects will be required to attend a clinic visit prior to randomization and must bring to the clinic their e-cigarettes or devices that they used daily in the screening diary so that the clinical site can record specifically what they used (including product type, flavor, nicotine level, and average daily use). At this clinic visit, each subject must establish a quit date that will in turn determine the date of study randomization and initiation of treatment. The quit date must be within 7-14 days of starting treatment and treatment must begin on the day after randomization.

Subjects will be provided with nicotine cessation counseling beginning on the clinic visit during screening prior to randomization (setting quit date and plan), again on the day of study randomization, and continuing weekly through the Week 12 visit.

Compliance will be assessed during the Treatment Period by reviewing each subject's diary (date and time of dosing) as well as ongoing drug accountability at each weekly clinic visit.

Subjects will be assessed for vaping abstinence/cessation or reduction by self-report of vaping and with biochemical assessments documented weekly starting at Week 2 through Week 12 and at Week 16. Vaping cessation will be defined as weekly vaping abstinence for 4 consecutive weeks documented by a subject self-report of not vaping and by biochemical verification of saliva cotinine <10 ng/mL by a central laboratory. Vaping reduction will be assessed by evaluating quantitative saliva cotinine levels relative to baseline screening levels. Measurements for expired CO levels will be monitored and are expected to stay at baseline levels of under 10 ppm.

Subjects will be assessed for safety (vital signs, adverse event reporting and concomitant medications) on Day 7 (Week 1). Note: clinic will also contact subject via telephone on Day 1 of treatment to assess for any initial reported adverse events) and then safety assessments will occur weekly at each clinic visit during the Treatment Period. In addition to the above safety assessments, hematology and chemistry assessments will be made on Day 7, Week 6 and Week 12 during the Treatment Period. Adverse events will be monitored through the Follow Up period. Safety monitoring during the study will be performed by an independent Data Safety Monitoring Committee (DSMC) composed of at least 2 independent experts in

the relevant therapeutic field. At Week 16 any adverse event or abnormalities considered to be clinically significant by the investigating physician will be followed with appropriate medical management until values are considered to be clinically acceptable or deemed chronic.
Statistical Considerations: *Analysis Sets* *Screening Analysis Set:* The Screening Analysis Set is defined as all subjects who give written informed consent and have entered screening but are not randomized. Analyses in this population will be restricted to presentation of baseline data and reasons for non-participation only. *Safety Analysis Set:* The Safety Analysis Set (SAS) is defined as all randomized subjects who take at least one dose of study drug. All safety analyses will be performed on the Safety Analysis Set. *Efficacy Analysis Set:* The All Randomized Analysis Set (ARS) is based on the 'intention-to-treat' principle and will include data from all randomized subjects. *Efficacy Outcomes* General efficacy outcomes will assess for vaping abstinence/cessation, or reduction in vaping. Weekly vaping assessments will start at Week 2 and continue weekly through Week 12. The primary efficacy measure will be the number of subjects who achieve vaping abstinence for 4 consecutive weeks from Week 9 to Week 12 by self-report of no vaping each week and supported by biochemical verification (saliva cotinine <10 ng/mL). Secondary efficacy outcomes: The number of subjects who achieve vaping abstinence at any time between Week 2 and Week 12 (e.g., self-report of no vaping in the past 7 days supported by biochemical verification) will also be reported as 7-day point prevalence rates. Other earlier time periods for achieving vaping cessation (e.g., vaping abstinence for 4 consecutive weeks from Week 3 to 6 or from Week 6 to 9) will also be assessed. The number of subjects who achieve continuous vaping abstinence at Week 9 through Week 16 (e.g., self-report of no vaping supported by biochemical verification). Measurements for CO levels will be monitored as a sensitivity test to assess that no concurrent combustible cigarette usage was used in those subjects reporting vaping abstinence or cessation. Other secondary efficacy outcomes for any reduction in vaping will be primarily assessed on a weekly basis between Week 2 and Week 12 using quantitative saliva cotinine levels when compared to baseline levels. *Other Outcomes:* All outcomes, including time to vaping abstinence, magnitude of treatment effect across subsets defined by demographic (e.g., gender, age) and/or baseline characteristics (e.g., e-cigarette product type, nicotine addiction severity), etc., will be performed as other exploratory assessments. In addition, the possible confounding effect of marijuana use on the ability to reduce nicotine vaping or cessation will be explored.

Statistical Methods

The overall study intent is to obtain effect outcomes and conduct additional safety assessments for efficacy and safety endpoints that will be used to inform the design of future studies. Thus, this study will be analyzed without specific statistical criteria. That is, no formal statistical hypothesis testing will be conducted, and consequently, a level of significance (α level) is not specified in the Statistical Analysis Plan (SAP). There will be statistical testing performed with p-values, and confidence intervals (CIs) to be computed. The p-values will be interpreted as an assessment of consistency with the play of chance (small p-values indicating a small likelihood that the observed effect was due to chance) and will be used qualitatively in decisions concerning next steps.

Trial Size

The target accrual is for approximately 150 subjects (100 subjects treated with cytisinicline and 50 subjects treated with placebo) which should be adequate to obtain additional safety assessments as well as explore various measures of cytisinicline effect outcomes compared to placebo.

Safety

The profiles of adverse events for the arms with regard to incidences of treatment emergent adverse events will be assessed. Treatment emergent adverse events are defined as those events that appear during treatment or are present before treatment and subsequently worsen. Laboratory, vital signs and ECG data will primarily be assessed for clinical safety. Data will be listed and summarized for each treatment according to measurement time.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION/TERM	DEFINITION
ACh	Acetylcholine
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ARS	All Randomized Analysis Set
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice a Day
BMI	Body Mass Index
CI	Confidence Interval
Cmax	Maximum Observed Plasma Concentration
CO	Carbon Monoxide
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DDI	Drug-to-Drug Interaction
DSMC	Data Safety Monitor Committee
ECG	Electrocardiogram
EVALI	e-cigarette or vaping use-associated lung injury
ET	Early Termination
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
HED	Human Equivalent Dose
ICH	International Conference on Harmonization
I.D.	Identification
IMP	Investigational Medicinal Product (for this protocol indicates cytisinicline 3 mg film coated tablet)
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MNWS	Minnesota Nicotine Withdrawal Scale
nAChRs	Nicotinic Acetylcholine Receptors
NRT	Nicotine Replacement Therapy
NOAEL	No-Observed-Adverse-Effect-Level
OR	Odds Ratio
PSUR	Periodic Safety Update Reports
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

ABBREVIATION/TERM	DEFINITION
SAS	Safety Analysis Set
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SOC	MedDRA System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TID	Three Times a Day
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Event
ULN	Upper Limit of Normal
USAN	United States Adopted Names

1. INTRODUCTION AND BACKGROUND

1.1. History of the Investigational Product

Cytisine is a plant-based alkaloid isolated from seeds of *Cytisus laburnum* (Golden chain acacia) and has been used as a smoking cessation drug since the 1980's in Eastern and Central Europe, marketed by Sopharma, Sofia, Bulgaria).[2] The molecular structure of cytisine has similarities to nicotine and acetylcholine (ACh). Nicotine addiction results, at least in part, from its interaction with neuronal nicotinic acetylcholine receptors (nAChRs). Both cytisine and nicotine compete for these receptors.[3-5] Cytisine has high affinity and specificity for neuronal nicotinic ($\alpha_4\beta_2$) receptors.

Despite its widespread use, cytisine has not been market-approved for use outside Eastern and Central Europe. [redacted] In 2018, the United States Adopted Names (USAN) Council adopted "cytisinicline" as the nonproprietary, or generic, name for cytisine. In [redacted]

1.2. Nicotine Addiction, Vaping, and Impact on Health

Nicotine is an addictive substance that is rapidly absorbed. The drug distributes quickly and is thought to interact with nAChRs in the central nervous system (CNS).

Tobacco smoking contributes to some 9 million premature deaths each year worldwide.[9] One increasingly popular alternative to smoking cigarettes is the use of nicotine-containing e-cigarettes, or vaping, which delivers liquid nicotine into a mist or aerosol which is inhaled. This method of consumption avoids or lowers exposure to many of the toxic chemicals associated with cigarette smoke but may have other associated health and safety issues. The emerging use of e-cigarettes is resulting in a population of people addicted to a new source of nicotine.

According to the Annals of Internal Medicine, data reported in 2018 estimated that approximately 10.8 million American adults use e-cigarettes and half of these users are age 18-34 years.[1] The United States Food and Drug Administration, or FDA, considers e-cigarette use an epidemic, particularly in youth, and the National Institute on Drug Abuse, or NIDA, a division of the NIH, has tobacco/nicotine and vaping on their list of Drugs of Abuse. Not only does e-cigarette use come with risks of its own, but research has also shown that young adults who vape are more likely to start smoking combustible cigarettes later. The number of e-cigarette users continue to grow and while e-cigarettes have been viewed as safer than combustible cigarettes, e-cigarettes may sustain nicotine addiction and the long-term safety of e-cigarettes is still unproven.

In 2019, the Center for Disease Control (CDC), the U.S. Food and Drug Administration (FDA), state and local health departments, and other clinical and public health partners were investigating a national outbreak of severe cases of lung illnesses referred to as "e-cigarette, or vaping, product use-associated lung injury (EVALI)". The number of EVALI cases reported to CDC peaked during the week of September 15, 2019, with the weekly number of hospitalized patients steadily declining as of February 2020 (refer to: www.cdc.gov/lunginjury). As of February 18, 2020, a total of 2,807 hospitalized EVALI cases or deaths were reported to CDC from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands). Laboratory data showed that vitamin E acetate, an additive in some THC-containing e-cigarette, or vaping, products, was strongly linked to the EVALI outbreak. However, evidence was not sufficient to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC vaping products, in some of the reported EVALI cases. Although there is currently no molecular mechanism of nicotine involvement in causing EVALI cases, other chemical components in nicotine-containing vaping products can also not be ruled out.

Cigarette smoking has long been a known risk factor for cardiovascular and pulmonary diseases (CVPD), even though direct effects and molecular mechanisms of nicotine in the pathogenesis of these diseases have not been elucidated. There is evidence that cigarette smoke or direct nicotine inhalation has a role in disrupting the homeostasis of the renin-angiotensin system (RAS), which impacts the regulation of blood pressure and the development of CVPD. The literature suggests that nicotine alters the homeostasis of the RAS by upregulating the detrimental angiotensin-converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type 1 receptor axis and downregulating the compensatory ACE2/ANG-(1-7)/MAS receptor axis.[10]

Other publications have shown various direct and indirect effects of nicotine on the immune system which may result in increased pulmonary inflammation or risk of pulmonary infections in smokers and possibly vapers.[11-14] Recent hypotheses that smoking or vaping nicotine may result in more susceptibility to the effects of coronavirus infections will warrant further investigations for either a possible direct nicotine effect or due to underlying CVPD as a risk factor.

Regardless of the various risks, outcomes, or direct mechanisms, nicotine addiction remains a public health concern.

1.3. Cytisinicline for Treatment of Nicotine Addiction

Prior trials have demonstrated cytisinicline's efficacy in helping people deal with nicotine addiction and to quit smoking. Cytisine was evaluated in three large, randomized Phase 3 clinical trials that were conducted according to Good Clinical Practice (GCP) in more than 2,000 participants. The overall objectives in these trials were to confirm the efficacy and safety of cytisine according to current clinical development standards.

The Phase 3 trial (TASC[6] trial) was sponsored by the UK Centre for Tobacco Control Studies and evaluated cytisine versus placebo in 740 primarily moderate-to-heavy smokers treated for 25 days in a single center in Warsaw, Poland. The primary outcome measure was sustained, biochemically-verified smoking abstinence for 12 months after the End-of-Treatment. The TASC trial was conceived by Professor Robert West (Department of Epidemiology and Public Health, University College London) and was funded by a grant from the National Prevention Research Initiative, including contributions from Cancer Research UK, Medical Research Council, United Kingdom Department of Health, and others. The results of the TASC trial were

published in the New England Journal of Medicine in September 2011.[6] The Relative Risk (RR) for sustained 12-month abstinence was 3.4 for cytisine compared to placebo (8.4% cytisine arm compared to 2.4% placebo arm; P<0.001). The RR for sustained 6-month abstinence was 2.9 (10.0% cytisine arm compared to 3.5% placebo arm; P<0.001). Cytisine was well tolerated with an increase in all-combined gastrointestinal (GI) adverse events (although there was no significant difference in individual GI events between the arms). The safety profile of cytisine was similar to that of a placebo, with no overall difference in the rate of side effects in the two arms.

The second Phase 3 trial (CASCAID[7] trial) was conducted by the Health Research Council of New Zealand and was an open-label trial that randomized 1,310 adult daily smokers. Subjects were randomized to receive either cytisine for 25 days or NRT for 8 weeks. Both treatment groups were offered low-intensity telephone behavioral support during trial treatment. The primary outcome measure was continuous self-reported abstinence from smoking one month after a quit date. The RR for continuous one-month abstinence was 1.3 for cytisine (40% cytisine arm compared to 31% in the NRT arm; P<0.001). A secondary outcome included the RR for continuous six-month abstinence which was 1.4 for cytisine (22% cytisine arm compared to 15% in the NRT arm; P=0.002). Cytisine was generally well tolerated, although self-reported adverse events were higher in the cytisine arm compared with the NRT arm. The most frequent adverse events were nausea and vomiting and sleep disorders. The results of the CASCAID trial, which were published in the *New England Journal of Medicine* in December 2014, showed that cytisine was superior to NRT for smoking cessation and, specifically, that cytisine was 1.43 times more likely than nicotine gums or patches to help participants stop smoking and remain non-smokers for six months.[7]

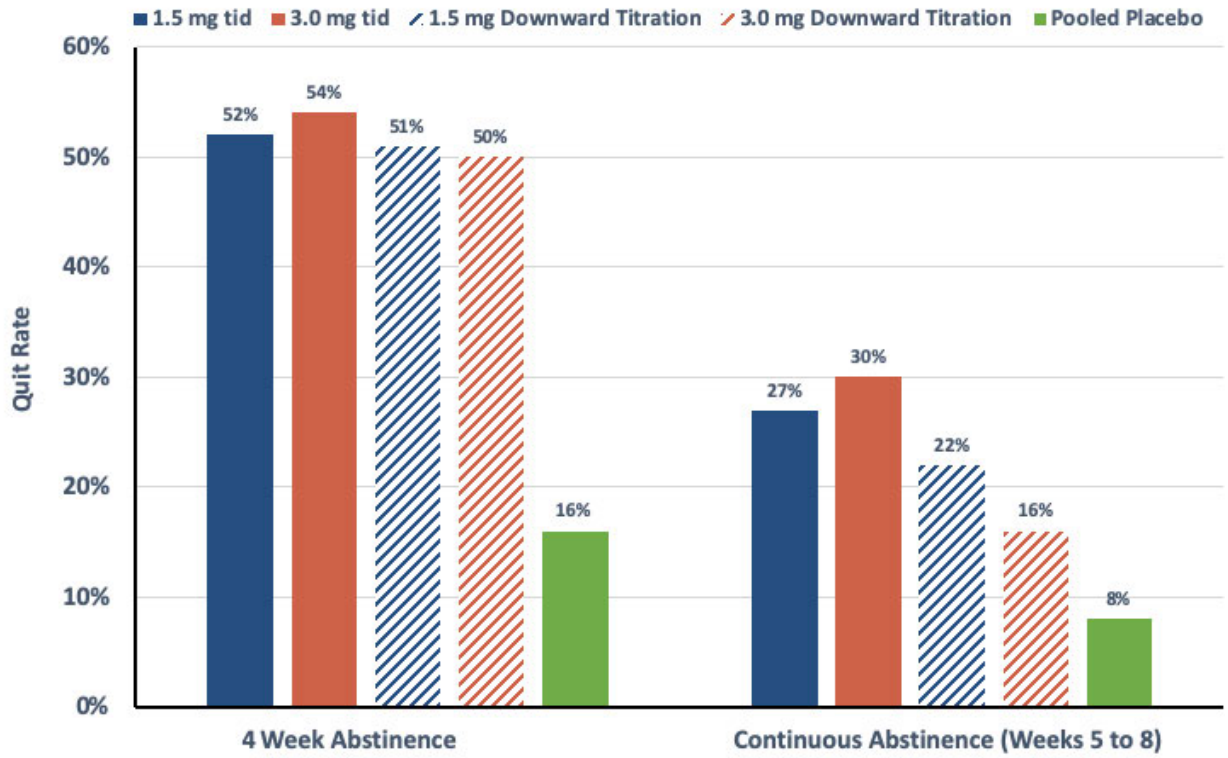
A recent third Phase 3 trial (RAUORA[8] trial) was conducted by Natalie Walker in New Zealand to determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥6 months in the New Zealand indigenous Māori or *whānau* (extended-family) of Māori, given the high smoking prevalence in this population. The study design was a pragmatic, open-label, randomized, community-based non-inferiority trial. Adult daily smokers who identified as Māori or *whānau* of Māori, motivated to quit in within 2 weeks, aged ≥18 years, and eligible for subsidized varenicline were enrolled and 679 people were randomly assigned (1:1) to receive a prescription for 12-weeks of cytisine or varenicline, plus low-intensity cessation behavioral support. Cytisine was administered first via the 25-day downward titration regimen followed by a daily maintenance of 1.5mg cytisine twice a day for the remaining 12 weeks and varenicline was administered for 12 weeks per market approved prescription. The primary outcome was carbon-monoxide verified continuous abstinence at 6 months, analyzed as intention to treat (with multiple imputation for missing data). Secondary outcomes included adverse event analyses. Verified continuous abstinence rates at 6 months post-quit date were 12.1% (41 of 337) for cytisine vs 7.9% (27 of 342) for varenicline (risk difference 4.29%, 95% confidence interval [CI] -0.22 to 8.79; relative risk 1.55; 95% CI 0.97 to 2.46). Sensitivity analyses confirmed the findings were robust. Self-reported adverse events over 6 months occurred significantly more frequently in the varenicline group (cytisine: 313 events in 111 participants; varenicline: 509 events in 138 participants, incidence rate ratio 0.56, 95% CI 0.49 to 0.65, p<0.001) compared with the cytisine group. Common adverse events were headache, nausea, and difficulty sleeping. The results of the RAUORA trial, which were published in *Addiction* in March 2021, showed that cytisine was at least as effective as

varenicline at supporting smoking abstinence in New Zealand indigenous Māori or *whānau* (extended-family) of Māori, with significantly fewer adverse events.

Achieve recently conducted a Phase 2b study that evaluated cytisinicline dosing using different administration schedules within the 25-day treatment period.[15] The Phase 2b study arms consisted of the 1.5 mg dose/downward titration schedule (used in the above Phase 3 studies and currently marketed in European countries), a higher dose of 3 mg using the same downward titration schedule, as well as a 1.5 mg and 3 mg dose using a simplified three times a day (TID) schedule, and respective placebo arms. Of the 254 subjects enrolled in the study, 121 (47.6%) were men and 133 (52.4%) were women. The mean (SD) age was 48.4 (13.0) years. For all Subjects, the mean (SD) number of years as a smoker was 32.1 (13.7), with an average of 18.2 (6.0) cigarettes smoked per day. All subjects in the study attempted to quit smoking in the past, with an average (SD) of 4.5 (4.8) previous quit attempts. The mean (SD) number of years from the last quit attempt to the first screening visit was 3.7 (5.1).

Below are the most relevant efficacy results for abstinence rates at Week 4 and prolonged abstinence (smoking cessation) through Week 5-8. The respective titration placebo and TID placebo arms were pooled based on demonstrating the same efficacy outcome measures. Treatment compliance was high for all arms with >94% mean compliance for study drug administration.

Figure 1: ORCA-1 Study: CO-Verified Abstinence Results



Results for the initial quit rate at Week 4 demonstrated both arms of the TID schedule had significantly higher odds of success of quitting smoking compared with placebo; subjects in the 3 mg cytisine arm had the best odds of success for quitting smoking: OR: 6.31 (95% CI: 2.28, 18.45). The OR for the 1.5 mg cytisine arm on the TID schedule was 5.81 (95% CI: 2.12, 16.87). On the commercial schedule, the ORs for the 1.5 and 3 mg cytisine arms were 5.59 (95% CI: 2.03, 16.29) and 5.38 (95% CI: 1.95, 15.72), respectively.

For smoking cessation from Week 5 to Week 8, both arms of the TID schedule had higher odds of success for abstinence compared with placebo; subjects in the 3 mg cytisine arm had the best odds of success for abstinence from Weeks 5 to 8, with an OR of 5.04 (95% CI: 1.42, 22.32). The OR for the 1.5 mg cytisine arm on the TID schedule was 4.33 (95% CI: 1.21, 19.30). On the commercial schedule, the ORs for the 1.5 mg cytisine and 3 mg arms were 3.23 (95% CI: 0.86, 14.85) and 2.24 (95% CI: 0.55, 10.82), respectively.

Subjects in the cytisine arms on the TID schedule also had higher odds of smoking abstinence at the Week 6, 7, and 8 timepoints compared with subjects in the corresponding arms on the commercial schedule versus placebo, as demonstrated by higher ORs at each timepoint.

All safety profiles appeared acceptable, especially for the 3mg TID schedule as shown below for the most common (>5%) adverse events.

Table 1: ORCA-1 Study: Most Common Adverse Events

	Downward Titration		**TID**		
	1.5 mg (n=51)	**3 mg (n=50)**	**1.5 mg (n=52)**	**3 mg (n=50)**	**Pooled Placebo (n=51)**
At least 1 AE	29 (57%)	23 (46%)	20 (39%)	21 (42%)	24 (47%)
Nausea	5 (10%)	3 (6%)	1 (2%)	3 (6%)	5 (10%)
Abnormal dreams	4 (8%)	7 (14%)	4 (8%)	3 (6%)	1 (2%)
Insomnia	3 (6%)	4 (8%)	4 (8%)	3 (6%)	1 (2%)
Headache	1 (2%)	1 (2%)	6 (12%)	2 (4%)	2 (4%)
URTI	3 (6%)	2 (4%)	5 (10%)	3 (6%)	7 (14%)

Refer to the Investigator's Brochure for more detail on GCP-conducted clinical studies by Achieve Life Sciences.

2. SAFETY OVERVIEW FOR CYTISINICLINE

2.1. Non-Clinical Studies

The US National Center for Complementary and Integrative Health (NCCIH) designated cytisine as "*a drug of national Public Health importance*" and, in collaboration, has sponsored a series of recent pharmacology and toxicology studies in support of the cytisinicline IND. In that regard, NCCIH has sponsored non-clinical GLP studies that have included 28-day repeat dosing for toxicology assessments in rats and dogs as well as reproductive/developmental studies in rats and rabbits. Achieve has also completed a 26-week chronic toxicology study in rats and a 39-week chronic toxicology study in dogs.

Results from the 26-week and 39-week chronic toxicology and the reproductive/developmental

[redacted]

[redacted]

2.2. General Safety of Cytisine as a Marketed Product

Cytisine has been marketed for many years by Sopharma in Central and Eastern Europe (including four countries in the European Union). It is estimated to have treated over 21 million smokers worldwide. Periodic Safety Update Reports (PSURs) have been submitted to the relevant European and national authorities following the European and local regulations and requirements.

[redacted]

Thus, from marketing safety reporting for cytisine, the most frequent adverse effects include: nausea, gastrointestinal symptoms (including abdominal pain, dyspepsia, and dry mouth), sleep disorder, dizziness and headache. Most reported adverse effects appear mainly at the beginning of therapy, are short-lived, mild-to-moderate intensity, and resolved spontaneously. It is not possible to dissociate these effects due to cytisine and those related to nicotine withdrawal.

2.3. Special Populations

Safety or pharmacokinetic information for the administration of cytisine in subjects with coronary disease, cardiac insufficiency, arterial hypertension, cerebrovascular diseases, hyperthyroidism, peptic ulcer, diabetes, renal, or hepatic insufficiency have not yet been obtained. Exclusion criteria have therefore been developed with external clinical input to exclude subjects that may have, or are being treated for, these underlying medical conditions.

[redacted]

3. RATIONALE FOR THE STUDY

Cytisine can reduce the severity of nicotine withdrawal symptoms as well as inhibiting nicotine reward effects by targeting nicotinic acetylcholine receptors (nAChRs) in the brain. Cytisine has been used as a smoking cessation drug since the 1980's in Central and Eastern European countries, where initial clinical studies were conducted.

An increasingly popular alternative to smoking cigarettes is the use of e-cigarettes, or vaping, which delivers liquid nicotine into a mist or aerosol which is inhaled. This method of consumption avoids or lowers exposure to many of the toxic chemicals associated with cigarette smoke but may have other associated health and safety issues. The emerging use of e-cigarettes is resulting in a population of people addicted to a new source of nicotine.

According to the Annals of Internal Medicine, data reported in 2018 estimated that approximately 10.8 million American adults use e-cigarettes and half of these users are age 18-34 years. The United States Food and Drug Administration, or FDA, considers e-cigarette use an epidemic, particularly in youth, and the National Institute on Drug Abuse, or NIDA, a division of the NIH, has tobacco/nicotine and vaping on their list of Drugs of Abuse. Not only does e-cigarette use come with risks of its own, but research has also shown that young adults who vape are more likely to start smoking combustible cigarettes later in life.

Evidence exists for the role of cigarette smoke or direct nicotine inhalation in disrupting the homeostasis of the renin-angiotensin system (RAS), which has a role in regulating blood pressure and the development of CVPD. Publications have shown various direct and indirect effects of nicotine on the immune system which may result in increased pulmonary inflammation or risk of pulmonary infections in smokers and possibly vapers. Regardless of the various risks, outcomes, or direct mechanisms, nicotine addiction remains a public health concern.

The number of e-cigarette users continues to grow and while e-cigarettes have been viewed as safer than combustible cigarettes, e-cigarettes may sustain nicotine addiction and the long-term safety of and addiction to e-cigarettes is still unknown. While developing a questionnaire for assessing dependence to e-cigarettes,[16] a multivariate analysis showed that individuals who had used e-cigarettes longer had higher dependence scores, as did those using more advanced e-cigarette devices that were larger than a cigarette and had a manual button. Those using zero nicotine liquid had significantly lower e-cigarette dependence scores than those using 1-12 mg/ml nicotine and those using 1-12 mg/ml nicotine also scored significantly lower than those using 13 or greater mg/ml nicotine liquid ($p < .003$). Thus, e-cigarette dependence appeared to vary by product characteristics, liquid nicotine concentration, and length of time using e-cigarettes.

Prior trials have demonstrated cytisinicline's efficacy in helping people quit smoking. This clinical study will evaluate the potential benefit of cytisinicline in treating nicotine addiction among users whose only source of nicotine is via the use of e-cigarettes. Given the mechanism of action of cytisinicline, this study will assess whether cytisinicline given to users of nicotine-containing e-cigarettes but not combustible tobacco products (i.e., conventional cigarettes) can reduce nicotine dependence and promote vaping cessation or reduction. The study population of e-cigarette users only, not dual users who are also smoking combustible cigarettes, is intentional for this study in order to monitor expired CO levels for any reverting to combustible cigarette smoking, which would be viewed as increasing harm while reducing e-cigarette usage.

As an added value, this study will evaluate the same safety parameters as the planned Phase 3 studies to be conducted for regulatory approval of cytisinicline as an aid for cigarette smoking cessation and hence will add to the growing safety database for cytisinicline in subjects addicted to nicotine either via combustible or e-cigarettes.

Thus, in this study, subjects will be randomized 2:1 to receive either 3 mg cytisinicline TID for 12 weeks plus standard behavioral support (Arm B: cytisinicline TID) or placebo TID for 12 weeks plus standard behavioral support (Arm A: placebo TID). The primary outcome assessment will be nicotine vaping cessation during Weeks 9-12. In this study, all references to vaping means the use of nicotine-containing e-cigarettes or other nicotine-containing vaping devices. Vaping cessation is defined as weekly nicotine vaping abstinence for 4 consecutive weeks. Other timing for weekly vaping abstinence/cessation (e.g., Weeks 3-6 or Weeks 6-9) and any reduction in nicotine vaping will be analyzed as secondary outcomes. The safety profile for 3 mg cytisinicline administered TID for 12 weeks will also be evaluated.

4. STUDY OBJECTIVES

4.1. Primary Efficacy Objective

Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of nicotine vaping cessation from Week 9 to Week 12 post-randomization as compared to subjects randomized to Arm A (placebo TID for 12 weeks plus behavioral support).

4.2. Secondary Efficacy Objectives

1) Assess whether subjects randomized to Arm B (cytisinicline TID) can achieve vaping abstinence/cessation at any time during treatment or reduce their daily vaping as objectively measured with biomarkers of nicotine exposure compared to subjects randomized to Arm A (placebo TID). Specific Secondary Efficacy Objectives related to this are described below:
    - Assess whether subjects randomized to Arm A have a higher probability of achieving vaping cessation between Week 3 and Week 9 post-randomization (e.g., Week 3-6 or Week 6-9,) as compared to subjects randomized to Arm B.
    - To compare arms (Arm A vs Arm B) on 7-day point prevalence rates for vaping abstinence on a weekly basis from Week 2 to Week 12.
    - To compare arms (Arm A vs Arm B) for a reduction in nicotine vaping using weekly quantitative cotinine levels from Week 2 to Week 12.
2) Assess whether subjects randomized to Arm A have a higher probability for continuous vaping abstinence between Week 9 and Week 16 post-randomization (i.e., subjects achieving primary endpoint abstinence with continued abstinence through follow-up).

4.3. Other Objectives

Explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.

Evaluate for nicotine withdrawal symptoms at Weeks 1-4 and again for any possible withdrawal symptoms due to study drug discontinuation pre- and post-Week 12.

4.4. Safety Objectives

To evaluate the safety profile of 3 mg TID cytisinicline when administered for 12 weeks.

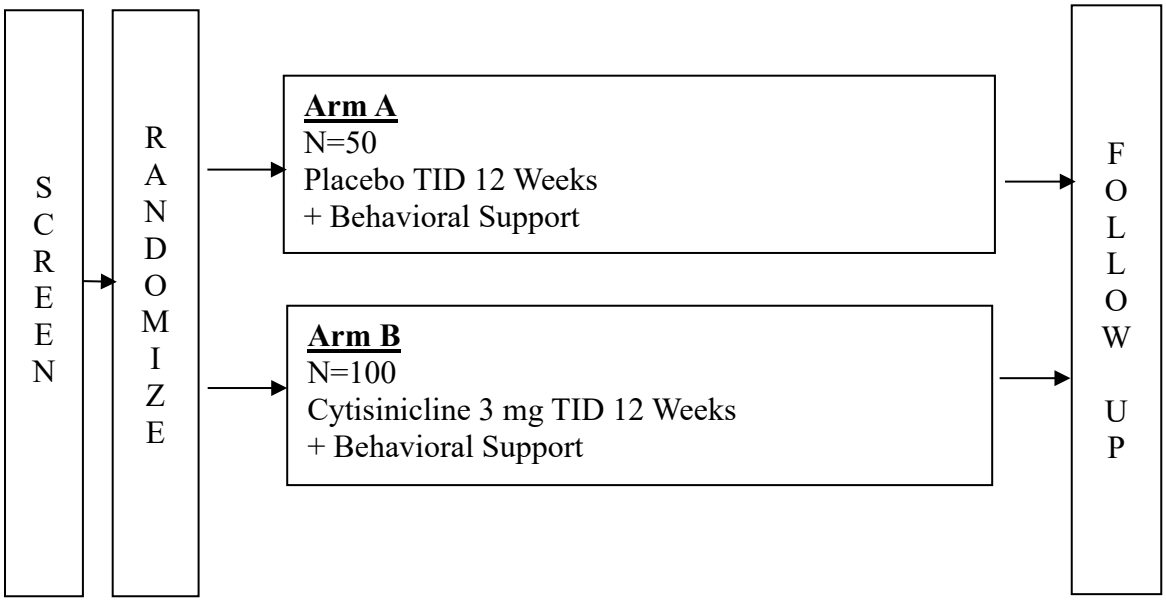
5. STUDY DESIGN OVERVIEW

5.1. Study Design

This will be a multi-center, double-blind, randomized, placebo-controlled, Phase 2 study conducted in male or female adults who are ≥18 years age and are daily nicotine e-cigarette users (i.e., vaping only subjects as confirmed with a positive cotinine sample ≥30 ng/mL and a carbon monoxide [CO] breath sample <10 ppm), intending to try to quit vaping, and willing to set a quit date that is within 7-14 days from the start of study treatment. Study treatment must start the day after study randomization.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. A total of approximately 150 subjects will be randomly assigned (2:1) to one of two arms: (Arm B, cytisinicline plus behavioral support: N=100 or Arm A placebo plus behavioral support: N=50) as shown in the study design figure below.

Figure 2: ACH-CYT-10 (ORCA-V1) Study Design Overview



The study will be conducted at approximately 5-8 clinical sites across the United States. Subjects will be randomized and stratified based on whether they have smoked >100 cigarettes in their lifetime (yes vs no).

The study will be comprised of a pre-study screen, followed by 12 weeks of treatment, and one post-treatment follow up visit at 16 weeks post-randomization.

Each randomized subject will receive 12 weeks of treatment using a TID dosing schedule. Vaping quit status (abstinence) will be assessed starting at Week 2 (Day 14±1) and assessments will continue weekly during the Treatment Period through to Week 12 and at Week 16. In addition, periodic assessments for cotinine in saliva and expired CO levels will be performed during the treatment period and will be compared to baseline (Day 0) measures. All subjects will receive concurrent nicotine cessation behavioral support during the study Treatment Period (Week 1-12).

Determination of vaping abstinence will be made from the subject's self-report of no vaping in the past 7 days with biochemical cotinine verification (cotinine <10 ng/mL). Weekly vaping assessments will start at Week 2 and continue weekly through Week 12. At the Week 16 follow up visit, expired CO will be measured and for those subjects reporting vaping abstinence, a saliva sample for cotinine testing will be assessed.

The primary efficacy measure will be the number of subjects who achieve nicotine vaping abstinence for 4 consecutive weeks from Week 9 to Week 12 (i.e., vaping cessation). The number of subjects who achieve vaping abstinence at any time between Week 2 and Week 12 will also be reported as 7-day point prevalence rates. Other secondary efficacy outcomes for achieving earlier vaping cessation (e.g., vaping abstinence for 4 consecutive weeks from Week 3 to 6 or from Week 6 to 9) will be assessed. Measurements for CO levels will be used as a sensitivity test to assess for concurrent combustible cigarette usage in those subjects reporting vaping abstinence or cessation. The number of subjects who achieve continuous vaping

abstinence at Week 9 through Week 16 (e.g., self-report of no vaping supported by biochemical verification).

Additional secondary efficacy outcomes for any reduction in vaping will be assessed on a weekly basis between Week 2 and Week 12 of cytisinicline treatment using quantitative saliva cotinine levels compared to baseline levels, as conducted by the central lab.

Subjects will be instructed to complete the Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire (Appendix 6) electronically at the Week 1, 2, 3, 4 clinic visits and again at 3 (±1) days prior to the Week 12 clinic visit and 3 (±1) days after the Week 12 clinic visit.

Safety assessments at clinic visits will occur on Day 7 (Week 1) and then weekly throughout the Treatment Period. Laboratory hematology and chemistry assessments will be made on Day 7, Week 6, and Week 12 during the treatment period. Adverse events will be monitored through the Follow-up Period. Any ongoing adverse events at Week 16 will be followed until resolved or determined to be chronic.

Treatment assignment unblinding for subjects will not occur until the end of the study has been reached, the database has been locked, and final study analyses have been performed, unless defined as an unblinding exception in Section 5.3.4.

5.2. Treatment Period (12 Weeks)

Treatment Period must begin on the day after randomization. Study treatment will be blinded, and subjects will take one study tablet three times during the day, approximately 5 hours apart. Subjects randomly assigned to Arm B will take one cytisinicline tablet at each dosing per day for 12 weeks. Arm A subjects will take one placebo tablet at each dosing per day for 12 weeks.

5.3. Discussion of Study Design

5.3.1. Placebo Control

A placebo control in this study design is necessary to control for response bias in evaluating for vaping abstinence and safety. Behavioral support alone has been shown to be effective in helping cigarette smokers to quit their nicotine addiction. Therefore all subjects in this study will receive behavioral support to aid their attempt to quit their nicotine vaping addiction. In addition, this study evaluates the effectiveness of cytisinicline when administered for 12 weeks compared to one placebo group, and the 2:1 randomization schedule means that subjects have a 2 in 3 chance of receiving active study drug. The use of a placebo group is therefore considered justified.

5.3.2. Primary Endpoint

The primary endpoint mirrors that used for smoking cessation trials. Smoking abstinence during the last 4 weeks of treatment with biochemically-verified CO levels has been the established primary endpoint for smoking cessation trials in regulatory approvals. Most Phase 3 trials had a “grace” period with success then determined by having 4 weeks abstinence during the last 4 weeks of treatment.

For the primary endpoint, success is defined as vaping abstinence during the last 4 weeks of the 12 week treatment period (Week 9 through Week 12) using quantitative saliva cotinine levels at <10 ng/mL for biochemical verification and subject's self-report of no vaping in the past 7 days.

5.3.3. Blinding

This double-blind study design protects against subjective bias in reporting both efficacy and safety. Blinding will occur by coding the individual study drug cartons and packs by an independent vendor assigned to the trial. The Sponsor and site personnel will not have access to the treatment assignment for individual subjects (except as an emergency; refer to Section 5.3.4) until the database is locked and final study analysis has been performed.

5.3.4. Unblinding

There is no intention to routinely unblind individual subjects at any time. During the study, emergency unblinding for treatment or regulatory reporting of adverse events might need to be performed as described below.

Unblinding may be done if the subject's well-being or treatment of adverse events requires knowledge of study drug assignment. The investigator must first contact the Study Medical Monitor, or representative, who will coordinate access to the treatment assignment code via the independent vendor.

Examples of unblinding for treatment emergencies include:

- A life-threatening, unexpected adverse event that is thought to be related to study drug and for which unblinding would change or influence treatment decisions.
- Medication error, such as an accidental overdose, that would warrant unblinding in order to more effectively manage toxicity.

Unblinding by the Sponsor may also be necessary to determine whether a serious and unexpected suspected adverse reaction (SUSAR) requires expedited reporting to FDA. Per FDA guidance, the sponsor must report an adverse event as a SUSAR only if there is evidence to suggest a causal relationship between the investigational drug and the adverse event such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
- One or more occurrences of an event that is not commonly associated with the investigational drug exposure, but is otherwise uncommon in the population exposed to the drug;
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational drug treatment group than in the concurrent control group.

Any unblinding of specific subjects by the Sponsor or required at the site level must be documented by the Sponsor.

5.4. Number of Subjects

A total of 150 subjects will be randomized to the study, with approximately 100 subjects in the cytisinicline arm and 50 subjects in the placebo arm. Efforts will be taken to coordinate weekly limits to enrollment rates and total enrollment numbers among the participating sites in order to ensure adequate subject management and similar enrollment distribution among sites. The maximum number of subjects that a single site may be allowed to enroll is 30% of the study total.

5.5. Randomization

Sites will utilize an Interactive Response Technology (IRT) system for treatment arm assignment at randomization (Day 0). The IRT will randomize and stratify subjects (lifetime >100 cigarettes smoked; yes vs no) across the study. Detailed instructions are provided in the Study Reference Manual.

5.6. Number of Clinical Sites

This will be a multicenter clinical trial within the US. Approximately 5-8 clinical sites will participate.

5.7. Estimated Duration/Completion of Study

Duration of this study is estimated to be approximately 16 weeks for an individual subject (from randomization to Week 16 visit). Completion of the entire study is dependent on accrual and is currently estimated at 8 months with ~2 months accrual ramp-up, an additional 2 months to complete accrual and 4 months for the last randomized subject to complete the study.

6. SELECTION OF STUDY POPULATION

Each potential subject will be provided with an informed consent form that has been reviewed and approved by the site's governing institutional review board (IRB). In accordance with the International Conference on Harmonization (ICH) guidelines on informed consent, the Investigator (or designee) will provide potential subjects with a verbal description of the study including, but not limited to, study purpose, study procedures, risks and duration. Potential subjects will be asked to read the consent form and to sign and date it once all of their questions have been answered and they voluntarily agree to participate in the study. A copy of the signed informed consent form will be provided to the subject.

Upon obtaining signed informed consent, each subject will undergo the screening procedures outlined in Section 10.2.1. A screening log will be maintained by the site and will include documentation for screening failures. Subjects meeting all inclusion/exclusion criteria will then be randomized to treatment and begin the study procedures. All subjects are considered enrolled once randomized.

This clinical trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

6.1. Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for inclusion into the study:

1. Male or female subjects, age ≥18 years.
2. Test positive for cotinine using the Alere iScreen® OFD Cotinine Oral Fluid Screening Device (Positive testing at ≥30 ng/mL cotinine level).
3. Current daily nicotine-containing electronic cigarette usage as recorded in a screening diary for at least 7 consecutive days. Willing to bring the e-cigarette or nicotine device used to the clinical site so that the specific product type, flavor, and nicotine level can be documented.
4. Willing to initiate study treatment on the day after randomization and set a quit date within 7-14 days of starting treatment.
5. Willing to actively participate in the study's vaping cessation behavioral support provided throughout the study.
6. Able to fully understand study requirements, willing to participate, and comply with dosing schedule.
7. Sign the Informed Consent Form.

6.2. Exclusion Criteria

Subjects meeting ANY of the following exclusion criteria will NOT be eligible for inclusion into the study.

1. Currently smoking, or having smoked within 4 weeks prior to study randomization, any combustible cigarettes, other combustible tobacco products or non-combustible tobacco products (such as heat not burn products) (i.e., dual users).
2. Expired Carbon Monoxide (CO) levels ≥10 ppm, indicating recent combustible tobacco use.
3. More than 1 study participant in same household during the study treatment period.
4. Known hypersensitivity to cytisinicline or any of the excipients.
5. Positive urinary drugs of abuse screen determined within 28 days before the first dose of cytisinicline (Note: THC is not part of the abuse screen).
6. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (i.e., requiring treatment or monitoring).
7. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (i.e., requiring treatment or further assessment).
8. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
9. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).

10. Documented diagnosis of schizophrenia or bipolar psychiatric illness; currently psychotic; having suicidal ideation within the last 3 months (corresponding to question 4 or 5 on the C-SSRS); or current symptoms of moderate to severe depression (depression score ≥11 on the HADS) within the last 3 months.
11. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation).
12. Hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
13. Recent history or symptoms (within 4 weeks of randomization) of unstable respiratory disease (e.g., pneumonia, product-use associated lung injury or EVALI, etc.)
14. Women who are pregnant or breast-feeding.
15. Male or female subjects of childbearing potential who do not agree to use acceptable methods of birth control starting at the time of consent, during the study treatment period, and continuing for one month after ending study treatment.
16. Participation in a clinical study with an investigational drug in the 4 weeks prior to study randomization.
17. Use of other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) in the 4 weeks prior to study randomization, any previous cytisine use, or planned use of these or other nicotine replacement medications during the study.
18. Any planned use during the study of combustible cigarettes or other nicotine-containing, non-vaping products (e.g., pipe tobacco, cigars, snuff, smokeless tobacco, hookah, ZYN pouches, etc).
19. Any other reason that the investigator views the subject should not participate or would be unable to fulfill the requirements for the study.

6.3. Modifying or Discontinuing Study Drug and/or Study Evaluations

6.3.1. Study Drug Modification during the 12-Week Treatment Period

Dose modifications in general are not allowed. On a case by case exception, the study treatment may be reduced to a twice a day (BID) schedule. These exceptions are only allowed for subjects who experience moderate or severe AEs (e.g., nausea, insomnia, nightmares, anxiety) that might be attributed to study drug and would otherwise discontinue study treatment due to the AE. The reduction of one dose from a TID to a BID schedule should be related to the timing of the moderate or severe AE. For example, removing the evening dose for AEs related to insomnia or nightmares OR removing the morning dose for nausea or other gastrointestinal symptoms related to possible fasting conditions. Any dose reductions need to be discussed and coordinated with the Study Medical Monitor, or representative, prior to any dose reduction. Once a dose reduction to a BID schedule occurs, no re-escalation back to a TID schedule is allowed. If the dose reduction to a BID schedule does not improve the AE symptoms to a tolerable level, then further dose reductions should not occur and the subject should discontinue study treatment.

6.3.2. Study Discontinuation

Subjects can be discontinued from study for the reasons below**:**

1. If a subject experiences a serious or intolerable adverse event that prevents the subject from continuing study drug.
2. At the Investigator's request (e.g., if the Investigator considers that the subject's health might be compromised by continuing study drug). Non-compliance should not be a reason for discontinuing treatment.
3. If a subject becomes pregnant during the study treatment period, study drug should be discontinued; however, the subject should be followed during the pregnancy for safety assessments.
4. At the request of the subject who does not want to continue study drug treatment or study evaluations.

The reason for discontinuation from study will be recorded in the CRF. If the subject discontinues prior to the Week 12 visit, safety assessments outlined for the Week 12 visit (C-SSRS, hematology and chemistry labs, ECG, HADS and urine pregnancy test if applicable) should be completed at the time of discontinuation.

If a subject discontinues study due to any adverse event or any abnormalities considered to be clinically significant by the investigating physician, the subject will be followed until values are considered to be clinically acceptable or deemed chronic.

7. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

7.1. Cytisinicline Film-Coated Tablets

Cytisinicline will be supplied by the Sponsor. The cytisinicline drug product is formulated as a compressed film-coated tablet containing 3 mg cytisinicline in a single tablet. Each tablet is composed of cytisinicline active substance (as the base) and well-established tablet-forming excipients. [redacted].

7.2. Placebo Tablets

Placebo tablets will contain the same excipients as in the cytisinicline tablet formulation plus additional cellulose powder in order to match final weight of the cytisinicline tablet. Placebo tablets will be identical in size, shape, color, and packaging in order to preserve the double-blind design of the study.

7.3. Receipt and Storage

The Study Drug will be supplied in 1-week treatment blister packs with 6 individual weekly blister packs in a carton (6 weeks of treatment). Each subject will be assigned 2 cartons for completing the 84 days (12 weeks) of study treatment. The first carton will be assigned on Day 0 and the second carton will be assigned on Day 35 (Week 5) so that treatment can follow assigned treatment arm (Figure 2). A clinical supplies management vendor will label, package, and distribute study drug to the sites.

Drug supply will be managed via an IRT program to maintain predetermined stock levels at the sites and/or handle resupply using site initiated requests. Upon receipt, details of study drug supplied shall be documented using the IRT and/or internal site login procedures.

The study drug shall be stored in a secure, temperature controlled location and only dispensed by suitably trained staff.

7.4. Administration

Study drug will be supplied as compressed tablets in blister packs. Tablets should be swallowed whole with water. Food does not influence the overall absorption of cytisinicline, so there are no restrictions on dosing with respect to the timing of meals.

7.5. Return/Destruction

At the end of the study, all unused study drug should be destroyed by the sites as directed by the Sponsor, unless a prearranged return to depot or to the Sponsor has been requested.

7.6. Method of Assigning Subjects to Arms

Subjects will be allocated to arms according to a predetermined randomization schedule and randomly assigned (2:1; with approximately 100 subjects in the cytisinicline arm and 50 subjects in the placebo arm.) once all screening procedures are completed and verified. Randomization will be stratified based on a prior history of having smoked >100 cigarettes in their lifetime (yes vs no).

The clinical research staff will record study drug (tablet) administration and all related information on the applicable source documents, to allow investigational product accountability and evaluation of subject compliance.

7.7. Study Drug Dosing Schedule

All subjects will receive 1 tablet for each of three dosing times, approximately every 5 hours per day. This 3 times a day (TID) schedule will be maintained for the 12 week treatment period.

Initial treatment Day 1 for the 12-week Treatment Period must start on the day after randomization.

7.8. Accountability

The pharmacist or pharmacist designee will maintain records of study drug receipt at the trial site, inventory at the site, dispensing for each subject, and any destruction or possible return of unused doses to the site for investigational product accountability.

Study drug for each subject will be configured into 2 coded study drug cartons, one of which will be assigned at randomization and the other will be assigned just prior to the Day 42 (Week 6) visit. Each carton will in turn contain 6 study drug packs and each pack will contain 21 tablets to cover 7 days (1 week) dosing. Clinic staff will distribute and collect the 7-day packs as the subject progresses through the clinic visits and will conduct ongoing accountability during each clinic visit by reviewing each subject's dosing timing in the diary and associated blister packs. Used packs will be retained so that the Sponsor's monitoring staff can verify accountability records.

Upon completion of the study, all the investigational study drug product that has not been used and all the empty containers of the used investigational product at the sites will be destroyed or returned to the depot or Sponsor.

8. PREVIOUS AND CONCOMITANT MEDICATIONS

All subjects will continue to receive any existing prescription medication. Every effort should be made to ensure that the regimen of existing medications remain stable during the study.

At the discretion of the Investigator, the use of non-study drug medications (either prescription or over-the-counter) may be given if clinically-indicated during the study. Full details of any new medications must be recorded in the subject's Case Report Form (CRF).

All concomitant medication(s) taken during the trial, and any changes (additions, deletions, dose changes) must be recorded in the CRF.

9. TREATMENT COMPLIANCE

Treatment compliance will be monitored during the 84 day (12 week) Treatment Period via review of dose timing and drug accountability. Subjects will have a daily diary that will record the number and time of tablets taken. Subjects will be instructed to bring their medication packs (blister packs) to each clinic visit so that clinic staff can reconcile against the diary, recording the number of tablets taken and the number of missed tablets. In addition, an optional text messaging system will be implemented that will provide each subject with reminder texts corresponding to the approximate time of dosing.

10. STUDY PROCEDURES

After providing signed informed consent, all subjects will be evaluated for inclusion in the study within a 28 day Screening Period. Subjects who meet inclusion criteria will be required to provide a quit date that must be within 7-14 days after the start of treatment and agree to initiating study treatment the day after randomization. Both planned quit and treatment start dates must be documented to confirm inclusion. Once all eligibility criteria are confirmed, randomization can occur. Study Day 1 will be defined as the first day of treatment. Subjects will complete a clinic visit on Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 86, plus one follow-up visit 4-weeks after completing study drug treatment.

10.1. Procedure Schedule

Table 3 provides a summary of required study evaluations. Refer to Section 10.2 for a detailed description of each study visit. Screening evaluations are to occur within a 28 day interval from initiation of screening evaluations to randomization. Subjects must initiate study treatment the day after randomization, such that study treatment is initiated on Day 1 prior to the quit date, within 7-14 days of Day 1.

Table 3: Schedule of Study Procedures During Treatment Period

Study Assessment	Screening Period (Day-28 to Rand)		Randomization	Treatment Period Week 1 – Week 12 (Day 84) (Days 7-86 are ±1 Day)													Follow-up
	SV 1[1]	SV 2[1]	Day 0[1]	D1[2]	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W5 (D35)	W6 (D42)	W7 (D49)	W8 (D56)	W9 (D63)	W10 (D70)	W11 (D77)	W12[3] /ET (D86)	W16 ±3 Days
Informed Consent	•																
Inclusion/Exclusion	•	•															
Demographics	•																
Medical and Psychiatric History	•																
C-SSRS Questionnaire[4]	•									•						•	
MNWS Questionnaire					•[16]	•	•	•							•[16]	•	
Physical Exam	•[5]																
Vaping History and Screening Vaping Diary completion	•[6]	•[6]															
Penn State Electronic Cigarette Dependence Index Questionnaire		•								•						•	
Marijuana Craving Questionnaire- Short Form		•														•	
Urine Pregnancy Test for all Females[7]	•		•					•				•				•	•
Drugs of Abuse Screen[8]	•																
Vital Signs including weight	•[9]		•		•	•	•	•	•	•	•	•	•	•	•	•	•
Hematology and Chemistry	•				•					•						•	
12-lead ECG	•									•						•	
Concomitant Medications	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Quit Date Set and Treatment Day 1 Scheduled		•															
Review Treatment Diary Completion Instructions			•	•													
Review Treatment Diary Entries for Completeness and Compliance[10]					•	•	•	•	•	•	•	•	•	•	•	•	

Study Assessment	Screening Period (Day-28 to Rand)		Randomization	Treatment Period Week 1 – Week 12 (Day 84) (Days 7-86 are ±1 Day)													Follow-up
	SV 1[1]	SV 2[1]	Day 0[1]	D1[2]	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W5 (D35)	W6 (D42)	W7 (D49)	W8 (D56)	W9 (D63)	W10 (D70)	W11 (D77)	W12[3] /ET (D86)	W16 ±3 Days
Adverse Event Reporting	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Study Drug Distribution, Accountability and Collection			•		•	•	•	•	•	•	•	•	•	•	•	•	
Behavioral Support		•[11]	•		•	•	•	•	•	•	•	•	•	•	•	•	
HADS Questionnaire	•[12]									•						•	
Vaping Abstinence Status						•	•	•	•	•	•	•	•	•	•	•	•
Cotinine[13]	•		•			•	•	•	•	•	•	•	•	•	•	•	•
Expired CO	•		•			•[14]	•	•	•	•	•	•	•	•	•	•	•
Use of any non-combustible nicotine products[15] and/or cigarette smoking						•	•	•	•	•	•	•	•	•	•	•	•

[1] Screening assessments used to evaluate inclusion and exclusion criteria can occur during 1 or more clinic visits over a 28-day period prior to randomization. Randomization *may* occur at the SV2 visit IF subject can commit to a quit date that allows start of treatment the following day. In such cases all Day 0 (Randomization) procedures must be completed at the SV2 clinic visit.

[2]Clinic will telephone each subject towards the end of Day 1 (first day of treatment) to make sure subject has taken medication according to dosing schedule, answer any questions, assess for adverse events and any concomitant medications and confirm the Day 7 clinic appointment.

[3]Procedures required at Day 86 or if subject discontinues treatment prior to Week 12.

[4] The Screening assessment for suicidal ideation (questions 1-5) will be asked within the past 3 months and the Suicidal Behavior questions will be asked within the past year. Assessments conducted at Week 6 and Week 12 will ask all questions since start of study.

[5]Physical exam may be conducted at either the SV1 or the SV2.

[6]Current daily electronic cigarette usage will be recorded in a 7-consecutive day vaping diary to be completed by the subject between SV1 and SV2. Adequate completion of the 7-day screening diary with verification of at least one vape per day is required for inclusion into the study. Documentation of specific products, nicotine level of devices/e-cigarettes will be recorded in the CRF.

[7]Urine pregnancy test kits supplied to site by central laboratory. All other testing performed by a central laboratory. Test results must be negative at the SV1 and D0 visit for inclusion into the study, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.

[8]Drugs of abuse to include at a minimum amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, opiates, and phencyclidine.

[9]To include height at screening for BMI calculation.

[10]Study subjects are to make daily treatment diary entries noting date and time of each dose. Sites are to review these prior (via on-line access) and during clinic visits to ensure subject is completing entries in real-time and accurately.

[11]Setting the quit date and plan is to be considered the first behavioral support counseling session.

[12]Depression questions to be scored within the HADS questionnaire in order to assess Exclusion Criteria #10.

[13]Saliva will be collected for cotinine determination. Screening will be based on the point-of-care Alere iScreen® OFD Cotinine Oral Fluid Screening Device (Positive testing at ≥30 ng/mL cotinine level). On-study cotinine determinations will be sent to a central laboratory for analysis. A post-treatment cotinine sample will be obtained at the Week 16 follow up visit.

[14]Any subjects with an expired CO level ≥10 ppm will be asked about combustible cigarette smoking as well as any cannabis smoking (see Section 12.3.2).

[15]Record any use of non-combustible nicotine products (other than vaping) and/or cigarette smoking.

[16] Subjects will be instructed to complete the Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire (Appendix 6) electronically at the clinic visit at Week 1, 2, 3, and 4 to determine any nicotine withdrawal symptoms. At the Week 11 clinic visit, subjects will be instructed that the MNWS questionnaire will also be administered electronically to all subjects 3 (±1) days prior to the Week 12 clinic visit and then 3 (±1) days after the Week 12 clinic visit to determine any similar withdrawal symptoms after completing cytisinicline.

10.2. Detailed Description of Study Visits

10.2.1. Screening Phase (SV1-SV2)

Screening assessments used to evaluate inclusion and exclusion criteria (SV1) can occur during 1 or more clinic visits over a 28-day period prior to randomization.

Screening (Day -28 to Randomization Day 0)

Study procedures include:

1. Written informed consent obtained.
2. Demographic data.
3. Medical and psychiatric history. Suicidal ideation is to be determined and documented via administration and assessment of the screening C-SSRS questionnaire (Appendix 1). Depression is to be assessed via the HADS questionnaire using the total for all depression-related questions (Appendix 2).
4. Physical examination.
5. Document any existing adverse events.
6. Document concomitant medications.
7. Review e-cigarette/vape use history, to include age started and number of days a nicotine vaping product was used in the past 30 days. In addition, identify all e-cigarette or vaping products used in the past 30 days and if more than one, the one most used, as well as the flavors used. Details about the specific products used, including nicotine concentration and typical weekly usage will be recorded.
8. Record if subject has attempted to quit e-cigarette smoking in the past and if they have, the number of times they had stopped vaping at least 1 day because they were trying to quit and the method(s) used in their quit attempt(s).
9. Record subject's reason for wanting to quit e-cigarettes, their level of desire to quit, and confidence in their ability to quit, as well as their perceived level of health risks from e-cigarettes compared to smoking cigarettes.
10. Identify if the subject has ever smoked a tobacco cigarette or smoked >100 cigarettes in their lifetime (Stratification Factor: "yes" versus "no"). Collect information about any previous use of combustible cigarettes (age started, average number of cigarettes smoked per day, how long since last smoked and methods/treatments used to quit). Inquire if the subject switched to nicotine-containing e-cigarettes in order to quit smoking cigarettes and how confident they are that they can continue to abstain from cigarettes in the future.
11. Record any other nicotine use, past and present.
12. Obtain saliva sample for cotinine level using the point-of-care Alere iScreen® OFD Cotinine Oral Fluid Screening Device to assess Inclusion Criteria #2 (Positive testing at ≥30 ng/mL cotinine).
13. Expired CO.

14. Vital signs, including weight and height for BMI calculation.
15. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
16. Drugs of abuse screen.
17. Hematology and Chemistry testing.
18. 12-lead ECG.
19. Provide diary instructions to capture specific type of daily e-cigarette use or vaping devices (e.g., types of pods, cartridges, single-use devices, etc.) for 7 consecutive days. This diary will be reviewed and recorded at Screening Visit #2 to verify that Inclusion #3 is met and document routine use. Note: Instruct subject to also bring into the clinic at Screening Visit #2, their device(s) and product(s) used during the 7-day screening diary period for further documentation.
20. Review all inclusion and exclusion criteria and if satisfied, schedule Screening Visit #2.

Screening Visit #2

1. Review all inclusion and exclusion criteria and if satisfied, continue with Screening Visit #2 procedures.
2. During the Screening Visit #2 document any existing adverse events and concomitant medications.
3. Subject to complete the Penn State Electronic Cigarette Dependence Index (Appendix 3) and the Short Form of the Marijuana Craving Questionnaire (Appendix 4).
4. Each subject is to complete an e-cigarette/vaping use diary and bring into the clinic their e-cigarette or device (including product type, flavor, product nicotine level) that they used on a daily basis during the 7-day screening diary. Clinic site personnel are to record the daily use for the 7 consecutive days and specifically what the subject used during the 7-day screening diary.
5. Each subject to provide their targeted quit date, which must be 7-14 days after randomization (Any Treatment Day between Day 7 to Day 14) and the targeted quit date must be documented. Setting a quit date and plan will be considered as the initial behavioral support session with the subject. The quit date will then determine the date for randomization. If a subject can commit to a quit date that allows for treatment to start the following day, the Screening Visit #2 may be treated as Day 0 and the subject can be randomized. In such cases, all procedures outlined in (Section 10.2.2) must be completed.

10.2.2. Randomization

Randomization (Day 0)

Randomization must be performed within 7-14 days prior to the agreed upon quit date. All other screening evaluations must be completed within 28 days prior to the Randomization Day. Study treatment must start on the day after randomization.

Study procedures include:

1. Update concomitant medication(s).
2. Document any existing adverse events.
3. Vital signs, including weight.
4. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
5. Obtain saliva sample for cotinine testing by central laboratory.
6. Expired CO.

Upon completion of procedures 1-6 above, assess for final confirmation/verification of eligibility If confirmation supports inclusion, complete the following:

1. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period.
2. Randomize according to a pre-determined, blinded, randomization schedule (see Section 5.5) and obtain the first study treatment carton (Carton #1) which will contain treatment packs for Weeks 1-6.
3. Provide study treatment Week 1 and Week 2 packs for the first 14 days of dosing and review dosing requirements. Review the layout and dosing instructions printed on the study treatment packs. Although packs will be marked with the week designation and dates, there will be times during the Treatment Period where a subject has multiple packs on hand. Review this with the subject and make sure it is understood that each pack must be completed for the designated time period before moving on to the next. Instruct subject that any/all packs in their possession must be brought back to the clinic at each visit and should never be thrown away. Used packs will be collected and all cartons and packs must be maintained by the site for drug accountability by the assigned study monitor.
4. Develop an appointment schedule that includes dates and times for each required clinic visit during the trial, providing a copy to the subject.
5. Provide study treatment diary instructions.
6. Schedule a time on the following day (Day 1 of treatment, late in the day) when clinic will contact subject to assess compliance, any possible adverse events and any changes/additions in concomitant medications.

10.2.3. Treatment Period

Treatment Day 1

All subjects must begin treatment on the morning of Day 1 and record all dosing in the treatment diary.

Clinic to contact subject via telephone call in afternoon or evening of Treatment Day 1 to:

1. Verify subject is taking treatment (one tablet three times a day), review treatment diary completion requirements and answer any questions.
2. Ask subject if any adverse events have occurred and/or any changes in concomitant medications.
3. Remind subject of their appointment time for the Week 1 study visit and that they must bring with them their study treatment packs.

Treatment Day 7/Week 1 (±1 day)

1. Reconfirm planned quit attempt date, which must be between Treatment Day 7 to 14.
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.
5. Review study treatment Week 1 pack for compliance. Ensure that subject has study treatment Week 2 pack covering the next 7 days and provide a study treatment Week 3 pack.
6. Provide subject with behavioral support information that includes counseling. (NOTE: it should again be stressed to subjects that even if they are vaping less or have quit vaping, they must maintain their dosing schedule throughout the Treatment Period.
7. Blood for hematology and serum chemistry testing.
8. Have each subject complete the Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire electronically at the clinic (Appendix 6).
9. Remind subject of their Day 14 (Week 2) appointment date and time and that they must bring with them all study treatment packs.

Treatment Day 14/Week 2 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 2 pack for compliance and collect the Week 1 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 3 pack and provide a study treatment Week 4 pack.

5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: At this time, it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit vaping. In addition, subjects are encouraged to continue trying to quit even if they are vaping or have a lapse after they have quit vaping.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.
8. Record the following:
    a. Has the subject vaped since the last clinic (Day 7) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 7) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Have each subject complete the MNWS questionnaire electronically at the clinic (Appendix 6).
10. Remind subject of their Day 21 (Week 3) appointment date and time and that they must bring with them all study treatment packs.

Treatment Day 21/Week 3 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 3 pack for compliance and collect the Week 2 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 4 pack and provide a study treatment Week 5 pack.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: At this time, it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit vaping. In addition, subjects must be counseled to be honest with their vaping status information and encouraged to continue trying to quit even if they are vaping or have a lapse after they have quit vaping.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.
8. Record the following:
    a. Has the subject vaped since the last clinic (Day 14) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 14) visit? If yes, record what was used and remind subject such products should not be used during the study.

9. Have each subject complete the MNWS questionnaire electronically at the clinic (Appendix 6).
10. Remind subject of their Day 28 (Week 4) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 28/Week 4 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 4 pack for compliance and collect Week 3 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 5 pack and provide a study treatment Week 6 pack, which will be the last pack in first carton (Carton #1) assigned at randomization.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit vaping. In addition, subjects must be counseled to be honest with their vaping status information and encouraged to continue trying to quit even if they are vaping or have a lapse after they have quit vaping.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
8. Expired CO.
9. Record the following:
    a. Has the subject vaped since the last clinic (Day 21) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 21) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Have each subject complete the MNWS questionnaire electronically at the clinic (Appendix 6).
11. Remind subject of their Day 35 (Week 5) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 35/Week 5 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.

4. Review study treatment Week 5 pack for compliance and collect Week 4 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 6 pack.
5. Obtain the study treatment carton #2 via IRT, which will contain study treatment Weeks 7-12 packs. Provide subject with a Week 7 pack from Carton #2.
6. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Again, it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit vaping. In addition, subjects must be counseled to be honest with their vaping status information and encouraged to continue trying to quit even if they are vaping or have a lapse after they have quit vaping.
7. Obtain saliva sample for cotinine testing by central laboratory.
8. Expired CO.
9. Record the following:
    a. Has the subject vaped since the last clinic (Day 28) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 28) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Remind subject of their appointment date and time for the Day 42 (Week 6) visit and that they must bring with them their study treatment packs.

Treatment Day 42/Week 6 (±1 day)

1. Administer and assess suicidal ideation/risk using the "Since Last Visit" C-SSRS questionnaire (refer to Appendix 1).
2. Subject to complete the HADS questionnaire (Appendix 2).
3. Subject to complete the Penn State Electronic Cigarette Dependence Index (Appendix 3)
4. Review study treatment diary to verify dosing up to time of visit.
5. Assess for AEs and any changes to concomitant medications.
6. Vital signs, including weight.
7. Review study treatment Week 6 pack for compliance and collect the Week 5 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 7 pack and provide a study treatment Week 8 pack from Carton #2.
8. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their vaping status information.
9. Blood for hematology and serum chemistry testing.
10. 12-lead ECG.

11. Obtain saliva sample for cotinine testing by central laboratory.
12. Expired CO.
13. Record the following:
    a. Has the subject vaped since the last clinic (Day 35) visit?
    b. If subject has vaped, record number of days subject vaped since the last visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 35) visit? If yes, record what was used and remind subject such products should not be used during the study.
14. Remind subject of their Day 49 (Week 7) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 49/Week 7 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 7 pack for compliance and collect the Week 6 pack (which was the last pack in Carton #1 and should be empty if all doses were taken as expected). Retain Carton #1 and all weekly packs for drug accountability by the study monitor. Confirm that the subject has the Week 8 pack and provide a study treatment Week 9 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their vaping status information.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.
8. Record the following:
    a. Has the subject vaped since the last clinic (Day 42) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 42) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 56 (Week 8) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 56/Week 8 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.

4. Review study treatment Week 8 pack for compliance and collect Week 7 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 9 pack and provide a study treatment Week 10 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their smoking status information.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
8. Expired CO.
9. Record the following:
    a. Has the subject vaped since the last clinic (Day 49) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 49) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Remind subject of their Day 63 (Week 9) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 63/Week 9 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 9 pack for compliance and collect the Week 8 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 10 pack and provide a study treatment Week 11 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining Treatment Period and to be honest with their vaping status information.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.
8. Record the following:
    a. Has the subject vaped since the last clinic (Day 56) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 56) visit? If yes, record what was used and remind subject such products should not be used during the study.

9. Remind subject of their Day 70 (Week 10) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 70/Week 10 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 10 pack for compliance and collect the Week 9 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 11 pack and provide the last study treatment Week 12 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining Treatment Period and to be honest with their vaping status information.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.
8. Record the following:
    a. Has the subject vaped since the last clinic (Day 63) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 63) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 77 (Week 11) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 77/Week 11 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 11 pack for compliance and collect the Week 10 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the last Week 12 pack.
5. Provide subject with behavioral support information that includes counseling (Appendix 5). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining week and to be honest with their vaping status information.
6. Obtain saliva sample for cotinine testing by central laboratory.
7. Expired CO.

8. Record the following:
    a. Has the subject vaped since the last clinic (Day 70) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 70) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 84 (Week 12) appointment date and time and that they must bring with them their study treatment packs.
10. Instruct subject that they will be notified to complete the MNWS questionnaire electronically 3 (±1) days prior to the Week 12 clinic visit (Appendix 6).

Treatment Day 84/ Week 12 (Day 86±1)

Note: The final day of treatment should be on Day 84. In order to ensure all subjects have completed treatment, the Week 12 visit is to be scheduled on Day 86±1 day.

1. Administer and assess suicidal ideation/risk using the "Since Last Visit" C-SSRS (refer to Appendix 1).
2. Subject to complete the HADS questionnaire (Appendix 2).
3. Subject to complete the Penn State Electronic Cigarette Dependence Index (Appendix 3) and the Short Form of the Marijuana Craving Questionnaire (Appendix 4).
4. Review study treatment diary to verify dosing through Week 12.
5. Assess for AEs and any changes to concomitant medications. NOTE: Any ongoing adverse events must be followed until resolved or determined to be chronic.
6. Vital signs, including weight.
7. Review study treatment Week 12 pack for compliance and collect both Week 11 and 12 packs (which should be empty if all doses were taken as expected).
8. Provide subject with behavioral support information that includes counseling (Appendix 5).
9. Blood for hematology and serum chemistry testing.
10. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
11. 12-lead ECG.
12. Obtain saliva sample for cotinine testing by central laboratory.
13. Expired CO.
14. Record the following:
    a. Has the subject vaped since the last clinic (Day 77) visit?
    b. If subject has vaped, record number of days subject vaped since the last clinic visit.
    c. Has the subject used any other combustible or non-combustible nicotine products since the last clinic (Day 77) visit?

15. Instruct subject that they will be notified to complete the MNWS questionnaire electronically 3 (±1) days after this Week 12 clinic visit and remind subject of their Week 16 Follow-up appointment date and time.

10.2.4. Follow-up Assessment

Week 16 (±3 days)

1. Assess for any AEs over the 4 weeks since completing study drug treatment.
2. Vital signs, including weight.
3. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.
4. Expired CO.
5. Record the following:
    a. Has the subject vaped since completing study drug treatment?
    b. If not, has the subject used any other combustible or non-combustible nicotine products?
6. Obtain saliva sample. Samples will be sent to a central laboratory for cotinine testing only for those subjects that have reported not vaping since completing the study treatment period.

10.2.5. Subject Diaries

A vaping diary will be collected during the screening period in order to capture daily e-cigarette use. These data will be used to support Inclusion Criteria #3 and document daily usage for at least 7 consecutive days on an individual basis.

In addition, a study treatment diary must be maintained by each subject to record date and timing of study drug administrations during the Treatment Period. The diary will be configured into specific sections to support the above reporting by the subject. Staff must review entries with the subject at each clinic visit and document on CRF. Data from the study treatment diary will be reviewed at all clinic visits.

10.2.6. Behavioral Support

Each participating site must have at least two or more staff members experienced and qualified to provide nicotine cessation counseling. For this study, site counselors are required to have either a master's level or higher degree in a counseling profession (e.g., health educator, chemical dependence counselor) or completed a nicotine treatment training course of at least 4 hours. Evidence of the above qualification(s) must be provided during the site qualification process.

All subjects will receive up to 14 behavioral support sessions by a qualified study site staff member, starting prior to randomization at the Screening Visit #2 when the subject sets their Quit Date, again at randomization and continuing through the End of Treatment (Day 86±1 day) visit as outlined in (Table 3). Each behavioral session will be subject-driven and must include direct

engagement with the subject about their attempt to quit vaping. Each session should last up to 10 minutes (Refer to Appendix 5).

Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they quit vaping as planned or if they lapse and have a puff after their quit date during the Treatment Period. It is also important to stress to subjects that they should be honest when reporting their vaping status and to remind them that all timepoints from Week 2 through Week 12 during the Treatment Period will be verified using cotinine levels.

11. EFFICACY CRITERIA

This study will follow general criteria that have been used in registration trials for smoking cessation where participants have a defined target quit date and there is face-to-face contact with researchers or clinic staff.[17] This vaping study will mirror criteria used for smoking cessation trials where smoking abstinence has been defined during the last 4 weeks of treatment with self-reported abstinence and verified by biochemical testing.

Vaping abstinence will be defined as a self-report of no nicotine-containing vaping in the past 7 days with biochemical saliva cotinine verification (cotinine <10 ng/mL). Weekly vaping assessments will start at Week 2 and continue weekly through Week 12.

The primary efficacy measure of nicotine vaping cessation will be the number of subjects who achieve vaping abstinence for 4 consecutive weeks from Week 9 to Week 12 by self-report of no vaping each week and supported by biochemical verification (saliva cotinine <10 ng/mL).

Efficacy analyses for vaping abstinence will include the following criteria:

1. Self-report of vaping abstinence since the last clinic visit at each weekly clinic assessment starting after the targeted quit week (Week 2 or Day 7-14).
2. Biochemical verification of nicotine abstinence by saliva cotinine levels at each clinic visit.
3. Use of an ‘intention-to-treat’ approach in which data from all randomized vapers are included in the analysis.
4. Subjects with an unknown vaping status at the Week 9 to 12 assessments or lost to follow up will be classified as failed to quit.
5. Continually blinded to treatment allocation during collection of all data and prior to database lock and final analyses.

Refer to Section 14.3 and Section 14.5 for the specific criteria in determining the primary and secondary efficacy outcomes, respectively.

12. SAFETY ASSESSMENTS

All subjects will be monitored for adverse events starting at screening (pre-existing), by telephone contact on Day 1, at clinic visits on Day 7 (Week 1), then weekly throughout the Treatment Period (Weeks 2 through 12). Adverse events will be monitored though the Follow-up Period. Any ongoing adverse events at Week 16 will be followed until resolved or determined to be chronic. Laboratory (hematology and chemistry) evaluations will be performed at the Week 1, Week 6, and Week 12 clinic visits using a central laboratory.

Safety will be assessed by consideration of all adverse events reported by or elicited from the subject and abnormalities detected on hematology and serum chemistry tests. Worsening of other preexisting medical conditions and any changes to concomitant medications/treatments will also be taken into account in this evaluation.

In addition to the planned times, safety procedures can be performed at any time when considered necessary by the Investigator or attending Research Physician.

In the event of any clinically significant abnormalities identified by the investigating physician, subjects will be followed until:

- It has resolved/returned to normal or baseline.
- The event has stabilized at a level acceptable to the Investigator and is not considered to be clinically significant.
- It has been shown to be chronic during follow-up assessment.

All adverse events (serious and non-serious) beginning at screening (prior to dosing) through the Week 16 visit will be recorded in the subject's CRF.

12.1. Definitions

An **Adverse Event** (AE) is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have attribution with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

An **Adverse Drug Reaction** (ADR) means all untoward and unintended responses to a medicinal product related to any dose administered. The phrase 'response to a medicinal product' means that attribution has at least a reasonable possibility, i.e., the relationship cannot be ruled out and is judged by the investigator as at least possible (see definition below).

An **Unexpected Adverse Drug Reaction** (UADR)/**Unexpected Adverse Event** (UAE) means an adverse reaction/event, the nature or severity of which is not consistent with the applicable product information, namely in the Investigator Brochure for an unauthorized investigational product or in the SmPC for an authorized product.

The expected/unexpected status should be evaluated and assessed, by the Sponsor, based on the reference safety information available since expectedness in Pharmacovigilance refers strictly to the information listed or mentioned in the applicable reference safety information and not to

event(s) that might be anticipated from knowledge of the pharmacological properties of a substance or because it was foreseeable due to the health status (e.g., age, medical history) of the study subjects.

A **Serious Adverse Event** (SAE) or **Serious Adverse Reaction** (SAR) is defined as an AE that results in any of the following:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongs existing inpatient's hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- Is an important medical event which requires medical intervention to prevent any of the above outcomes.

SUSARs: AEs which meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs):

- Serious.
- Unexpected (i.e., is not consistent with the applicable product information e.g., Investigator's brochure for an unapproved IMP or SmPC for an authorised product).
- There is at least a reasonable possibility that there is attribution between the event and the medicinal product.

Important medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolves without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

Inpatient **hospitalization** or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE or occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedures.

12.2. Recording of Adverse Events

All of the following details will be recorded in the subject's CRF for each AE:

- Full description of AE.
- Date and time of onset.
- Date and time of resolution.
- Severity of event, to be assessed by an Investigator, or their delegate, in accordance with the definitions below.
- Relationship to study drug to be assessed by an Investigator, or their delegate, in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

Adverse events documented in the CRF without a stop date at the Week 16 visit must be followed until final resolution or until it is medically justifiable to stop further follow up (e.g., a chronic condition has been reached.) Documentation of adverse events should be updated as necessary.

12.2.1. Grading Adverse Event Severity

The following grades will be used by an Investigator to describe the severity of all AEs (including clinically-significant laboratory AEs) as shown in Table 4. Only 1 severity grade will be used for each AE (e.g., mild - moderate is not acceptable).

Table 4: Adverse Event Severity

Severity of AE	Definition
Mild	No interference with activity
Moderate	Some interference with activity requiring no or minimal medical intervention
Severe	Prevents daily activity and requires medical intervention

If an adverse event has multiple aspects, the aspect with the highest intensity will be graded. It is emphasized that the term severe is a measure of intensity; thus a severe AE is not necessarily serious. For example, itching for several days may be rated as severe; however, may not be clinically serious.

12.2.2. Assessment of Attribution

The attribution between an adverse event and study drug will be determined and documented by the responsible Investigator, or their delegate, according to best medical judgment as shown in Table 5.

Table 5: Assessment of Attribution to Study Drug

Category	Description
Not Related	The event is definitely not associated with study drug.
Unlikely	The event was most probably produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy, and does not follow a known response pattern to study drug.
Possible	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product but could have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy.
Probable	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy.
Definite	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study drug administration, or improves on stopping the study drug.

12.2.3. Reporting of Serious Adverse Events

Any SAE that occurs during the AE reporting period (Screening to Week 16) must be recorded and reported immediately. All SAEs including those that are ongoing at the end of the Week 16 visit will be followed until each event resolves or is assessed as chronic.

In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed study drug-related or not, must be reported to the Sponsor or designee as soon as possible after the Investigator (or delegate) has become aware of its occurrence. SAE form completion and reporting must not be delayed, even if all of the information is not available at the time of the initial contact.

SAEs must be reported within 24 hours of knowledge of the event by submitting an initial SAE report via email, telephone or fax.

[redacted]

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available.

The following information should be provided to accurately and completely record the event:

- Investigator name and center number.
- Subject number.
- Subject initials.

- Subject demographics.
- Clinical event:
  - description.
  - date of onset.
  - severity.
  - treatment.
  - relationship to study drug (attribution).
  - action taken regarding study drug.
- If the AE resulted in death:
  - cause of death (whether or not the death was related to study drug).
  - autopsy findings (if available).
- Medical history case report form (copy).
- Concomitant medication case report form (copy).
- Any relevant reports (laboratory, discharge, x-ray, etc.).

Subjects who have had an SAE during the AE reporting period (Screening through to Week 16 visit) must be followed clinically until all parameters (including laboratory) have either resolved or been assessed as chronic.

SUSARs should be reported to the IRB (if applicable) and to the FDA in accordance with applicable regulatory requirements for expedited reporting. It is the Site's responsibility to report any SUSAR to their IRB and it is the Sponsor's responsibility to report any SUSAR to the FDA.

Full details of SAE handling and SUSAR reporting will be documented in a study specific reference manual prior to the start of dosing.

12.2.4. Reporting of a Pregnancy during Study Treatment

If a pregnancy occurs in a randomized subject (or the partner of an enrolled subject) during the study treatment or follow-up period, the Investigator must complete the Pregnancy Notification Form and submit to the CRO Pharmacovigilance Associate. Although not considered an SAE, the CRO PV Group will process pregnancy notifications using the same guidelines as for SAE reports above [i.e., will acknowledge receipt of any pregnancy notification (initial or follow up) within 24 hours of receipt to the site with a copy to the Medical Monitor and Sponsor for their awareness].

Since there may be unknown risks to a pregnancy, embryo, or fetus (Section 2.1.3), the pregnant subject should discontinue study drug treatment however the subject should be followed during the pregnancy for safety assessments.

The CRO PV Group will also follow up with the Investigator after completion of the study on the monitoring of the subject for the duration of the pregnancy and until 28 days after the child is

born. Any serious adverse events of the subject during the pregnancy or of the child at birth need to be recorded and CRO PV Group notified accordingly.

12.2.5. Reporting of COVID-19 Positive cases and COVID-19 vaccinations as Adverse Events of Special Interest

Subjects known to be COVID-19 positive during the study will be documented under adverse event reporting as AEs of special interest. In addition, any COVID-19 vaccinations should be documented during the study and any side effects immediately following a COVID-19 vaccination should be documented under adverse event reporting as AEs of special interest.

Any effects of the COVID-19 pandemic on the conduct of the study or any specific effects of COVID-19 infections or vaccinations on treatment arm results will be assessed.

12.3. Laboratory

12.3.1. Routine Laboratory Assessments

Routine laboratory safety samples will be analyzed at screening and at clinic visits as identified in (Table 3) for each subject by a central laboratory. A decision regarding whether a result outside the reference range is of clinical significance or not shall be made by an Investigator and the report will be annotated accordingly. Clinically significant abnormalities occurring during the study will be recorded on the AE page. The reference ranges for laboratory parameters should be filed in the TMF and the Investigator site file.

Hematology: Hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

Chemistry: Total protein, albumin, total bilirubin, SGPT (ALT), SGOT (AST), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine and urea.

12.3.2. Monitoring of Expired Air Carbon Monoxide (CO)

Expired CO will be obtained using a calibrated instrument (e.g., the Bedfont Micro+ Smokerlyzer®) provided and maintained by the clinical site. Each clinical site must have a minimum of 2 devices on hand, documentation of instrument used and current calibration. CO values are to be reported in parts per million (ppm) at Week 2, weekly through Week 12 and at Week 16.

This study excludes dual users (smoking and vaping nicotine) because smoking oversight is difficult to monitor for increased use of combustible smoking while reducing nicotine vaping. Nonsmoking at screening in this study is confirmed by standard expired CO levels <10 ppm. Ongoing monitoring for expired CO levels is included in this study to assess for the potential risk of a subject to start, or relapse into, smoking combustible cigarettes while trying to reduce or stop nicotine vaping. If smoking appears to become an issue, the Data Safety Monitoring Committee can recommend amending study procedures or close the study if the risk appears greater than the benefit of stopping nicotine vaping (see Section 13.1).

If expired CO levels ≥10 ppm are detected, the subject should be asked about combustible cigarette smoking including the start date of smoking. If the subject reports smoking combustible cigarettes, the total number of cigarettes smoked since the last clinic visit should be reported in

the CRF. If expired CO levels ≥10 ppm are detected and the subject reports not to have smoked combustible cigarettes, they should be asked about any cannabis smoking. If they report concomitant cannabis smoking, the number of days used since the last clinic visit should be reported in the CRF.

12.3.3. Cotinine Levels

Saliva samples will be collected for determining cotinine levels at Day 0 and again starting at Week 2 and weekly through Week 12 and at Week 16. Cotinine will be assessed using a quantitative saliva cotinine assay performed by a central laboratory and reported in ng/mL.

12.4. Vital signs

Systolic/diastolic blood pressure, pulse rate, and oral temperature measurements will be recorded in a seated position. Body weight will also be recorded. Height is to be recorded at Screening Visit #1 for BMI calculation.

12.5. Physical Examination

A physical examination will be performed by an Investigator. The examination will include general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, central nervous system, lymph nodes and musculoskeletal. An Investigator can examine other body systems if required, at their discretion.

13. SAFETY MONITORING

13.1. Independent Data Safety Monitoring Committee

Safety monitoring will be performed by an independent Data Safety Monitoring Committee (DSMC) who will be appointed for this study. The DSMC will be composed of at least 2 independent experts in the relevant therapeutic field and a third relevant expert such as a statistician.

The DSMC governance and operating procedures are described in a separate DSMC Charter. Meetings will be held via telecommunications equipment and will meet regularly in order to assess safety and trial status. Regular DSMC meetings will be planned during enrollment and while treatment is ongoing. Additional meetings will be at the discretion of the DSMC, and the meeting schedule may be altered at the request of the Sponsor or at the discretion of the DSMC Chairperson. Meetings will typically begin with an open session. DSMC members, representatives of the Sponsor and other individuals as needed may be present during the open session. The open session will be followed by a closed session. Only DSMC members, and other individuals, as needed by the DSMC, will be in attendance at the closed session.

The primary responsibility of the DSMC will be to monitor for any unexpected safety risk for subjects on the protocol. The DSMC will:

- Review all SUSARs and SAEs reported to the Sponsor. The Sponsor will provide the DSMC with a copy of any unexpected study drug-related SAE Report Form within 7 business days of receipt by the Sponsor. The Medical Monitor (or designee) will

also provide the DSMC with copies of all expedited SAE reports submitted to regulatory agencies.

- Perform periodic reviews of overall safety data for the study (e.g., moderate or severe adverse events).

  NOTE: Any respiratory symptoms, including cough, shortness of breath, or chest pain that are reported as moderate or severe will be reported to the DSMC within 7 business days of being reported to the Sponsor. The DSMC will review for possible further EVALI assessment or further follow-up.

- Specific reviews for subjects who may start or revert to smoking combustible cigarettes during study treatment will be assessed by the DSMC for any increased harm or risk to subjects. The timing of these reviews will be determined by the DSMC based on rate of enrollment and status of concern upon reviewing CO reports or reporting of combustible cigarettes by subjects during the study.

The DSMC may request unblinding of study treatment based on a safety concern or specific SUSARs or SAE. All unblinding and the reason for unblinding will be documented by the DSMC. The Sponsor and sites will not be unblinded unless the DSMC requests that individual or other unblinding occurs due to a safety concern.

The DSMC Chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the trial. The sponsor will work closely with the committee to provide the necessary data for review.

14. STATISTICAL CONSIDERATIONS

A major design feature of this study is blinding. The study will be unblinded only after database lock and at the time of final study analyses (i.e., when unblinding cannot induce bias in collection of data and interpretation of results).

Detailed statistical specifications are documented in the Statistical Analysis Plan (SAP) and the SAP will be final prior to initiation of any study unblinding.

14.1. Statistical Design

The overall study design is to obtain effect outcomes and conduct additional safety assessments and endpoints that will be used to inform the design of future studies. Thus, this study will be analyzed without specific statistical criteria. That is, no formal statistical hypothesis testing will be conducted, and consequently, a level of significance (α level) is not specified in the Statistical Analysis Plan (SAP). There will be statistical testing performed with p-values, and confidence intervals (CIs). The p-values will be interpreted as an assessment of consistency with the play of chance (small p-values indicating a small likelihood that the observed effect was due to chance) and will be used qualitatively in decisions concerning next steps.

14.2. Analysis Sets

Screening Analysis Set: The Screening Analysis Set is defined as all subjects who give written informed consent and have entered screening but are not randomized. Analyses in this population will be restricted to presentation of baseline data and reasons for non-participation only.

Safety Analysis Set: The Safety Analysis Set (SAS) is defined as all randomized subjects who take at least one dose of study drug. All safety analyses will be performed on the Safety Analysis Set.

Efficacy Analysis Set: The All Randomized Analysis Set (ARS) is based on the 'intention-to-treat' principle and will include data from all randomized subjects.

14.3. Primary Efficacy Outcome

The primary efficacy outcome for vaping cessation (defined as biochemically verified vaping abstinence for the last 4 weeks of cytisinicline treatment) for each subject is binary: success versus failure will be analyzed using the Efficacy Analysis Set. Success is defined for the subject as having reported vaping abstinence (no vaping since the last clinic visit) at each clinic assessment from Week 9 to Week 12 with biochemical cotinine verification at each assessment. Biochemical verification will be defined by saliva cotinine levels of less than 10 ng/mL. Similar timeframe and analyses will occur for both Arm A and Arm B subjects.

Any other outcome is regarded as a failure. There are two types of failure for a subject: (1) subjects with adequate data that they are vaping (either by the subject's self-report or cotinine levels ≥10 ng/mL) and (2) subjects having insufficient data to be determined as a success for vaping cessation. This definition of primary outcome means that all subjects will have a realization of the primary outcome and therefore this endpoint is amenable to intent-to-treat (ITT) analyses.

Measurements of CO levels will also be used for sensitivity testing to assess for any concurrent combustible cigarette usage in those subjects reporting successful vaping cessation.

14.4. Analysis of Primary Outcome

The outcome for each arm will be the proportion of subjects classified as a success. The experimental arm (Arm B) will be compared to the control arm (Arm A) at the appropriate timeframes. All randomized subjects will be included in the comparison according to their randomized arm (ITT analysis). The statistical significance of each comparison will be based on the odds ratio using exact computations for stratified 2×2 frequency tables and using Monte Carlo estimation if necessary. The stratifier will be whether subjects have smoked >100 cigarettes in their lifetime (yes vs no). If cytisinicline is not favored by the effect size point estimate then the comparison will be designated as not statistically significant.

The estimated common odds ratio and its exact confidence interval will be reported. In addition, the estimated odds ratio and exact confidence interval for the marginal 2x2 table across sites (unadjusted odds ratio), and the estimated difference in proportions and the associated derived exact confidence interval using the exact confidence interval on the odds ratio will be reported. The exact difference in proportion confidence interval is derived using the method of Thomas (1971 and 1977).[18,19]

In addition, the primary comparisons will be presented in the context of a tipping point analysis.[20] Other supporting and sensitivity analyses challenging the results as well as analyses designed to assess homogeneity of effect are planned and described in the SAP.

14.5. Secondary Efficacy Outcomes

Secondary efficacy outcomes will assess for weekly vaping abstinence, earlier vaping cessation timing, any reduction in vaping during the treatment period, and continued vaping abstinence during the 4 week follow-up period for those subjects who achieved vaping abstinence at Week 9 to 12 and through week 16.

Vaping abstinence will be generally defined as a self-report of no vaping in the past 7 days with biochemical cotinine verification (saliva cotinine <10 ng/mL). Weekly vaping assessments for vaping abstinence will start at Week 2 and continue weekly through Week 12.

As stated above, the primary efficacy measure of nicotine vaping cessation will be the number of subjects who achieve vaping abstinence for 4 consecutive weeks from Week 9 to Week 12 by self-report of no vaping each week and supported by biochemical verification (saliva cotinine <10 ng/mL). For the secondary analyses, the number of subjects who achieve vaping abstinence at any week between Week 2 and Week 12 (e.g., self-report of no vaping in the past 7 days supported by biochemical verification) will be reported as weekly point prevalence rates. Additional analyses will be done for earlier 4-week periods in achieving vaping cessation (e.g., vaping abstinence for 4 consecutive weeks from Week 3 to 6 or from Week 6 to 9).

Measurements for CO levels will also be used for sensitivity testing to assess that no concurrent combustible cigarette usage was used in those subjects reporting weekly vaping abstinence or vaping cessation.

Other secondary efficacy outcomes for any reduction in vaping will be assessed on a weekly basis between Week 2 and Week 12 of cytisinicline treatment using the quantitative saliva cotinine levels compared to baseline levels, as determined by the central lab.

14.6. Analysis of Secondary Outcomes

For the secondary endpoints of weekly vaping abstinence and earlier vaping cessation timing these will be analyzed the same as the primary endpoint analysis. For the reduction in vaping during the treatment period, this will be analyzed using an analysis of variance.

14.7. Study Size

The target accrual is for approximately 150 subjects (100 subjects treated with cytisinicline and 50 subjects treated with placebo) which should be adequate to obtain additional safety assessments as well as explore various measures of cytisinicline effect outcomes compared to placebo. Although no formal statistical hypothesis testing will be conducted, the sample size will have 95% power to detect a 57 ng/mL reduction in cotinine levels at baseline levels of 300 ng/mL (e.g., approx. 19% reduction from baseline).

14.8. Other Objectives

Other objectives beyond the designated primary and secondary objectives will be exploratory. All outcomes, including time to vaping abstinence, magnitude of treatment effect across subsets defined by demographic (e.g., gender, age) and/or baseline characteristics (e.g., e-cigarette product type, nicotine addiction severity), etc., will be performed as other exploratory assessments. In addition, possible confounding effects of marijuana use on the ability to reduce nicotine vaping or cessation will be explored as well as any withdrawal symptoms from discontinuing cytisinicline after 12 weeks of administration.

14.9. Safety Objectives

Safety assessments include reported adverse events, laboratory tests results, and vital signs. Safety variables will be summarized for the Safety Analysis Set (SAS), defined as all randomized subjects who take at least one dose of study drug.

Adverse events will be coded using the MedDRA dictionary. Coding includes system organ class (SOC) and preferred term (PT). All verbatim descriptions and coded terms will be listed for all AEs.

Safety summaries are described in the SAP.

15. REGULATORY AND ETHICS CONSIDERATIONS

15.1. Institutional Review Board (IRB)

This study protocol must be submitted to an IRB for review and approval prior to initiation. As this study will be conducted at multiple sites, it is expected that each site must submit and obtain approval from their designated IRB with preference towards use of a central IRB when at all possible. Before the investigational product can be shipped to the investigative site and before the consenting and screening of subjects at the site, the protocol, any protocol amendments, the consent form, any advertising materials, any materials to be provided to the subjects for the proposed clinical study, and any other documents required by the IRB must be submitted by the Investigator (or representative) for review and approval by the IRB. The Investigator must also ensure that the IRB reviews the progress of the study, if necessary, and renews its approval of the study (if ongoing) on an annual basis. Any member of the IRB who is directly affiliated with this study as an Investigator or as participating site personnel must abstain from the IRB vote on the approval of the protocol and associated documents.

All amendments or revisions to the protocol must undergo review by appropriate IRBs. Amendments/revisions will be circulated to all participating sites with clear instructions regarding IRB review. Amendments will be submitted by the Sponsor to the Food and Drug Administration (FDA) prior to central implementation to the study, and by IRBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or is of a purely administrative nature.

A copy of the IRB approval letter must be forwarded to the Sponsor or Sponsor’s representative before the study is implemented. The approval letter must clearly state the protocol title and

version that was reviewed, as well as any associated documents. The Investigator also must forward copies of subsequent amendment approval letters upon receipt.

15.2. Ethical Conduct of the Study

This trial will be conducted in accordance with the Declaration of Helsinki, as well as the ICH Guidelines on GCP, the US Code of Federal Regulations, and local requirements regarding IRB committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

15.3. Informed Consent

The informed consent forms used for the study must comply with the Declaration of Helsinki and its updates and the International Conference on Harmonization (ICH) Guidelines and must have been approved by the Sponsor or Sponsor's representatives (prior to review by the site's IRB) and the Investigator's IRB. The Investigator or an authorized associate, must explain the nature of the study and the treatment in such a manner that the subject is aware of his/her rights and responsibilities, as well as potential benefits and risks. The Investigator is also responsible for answering any questions the subject may have throughout the study and sharing any new information, in a timely manner, that may be relevant to the subject's willingness to continue his/her participation in the trial.

Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent should be recorded in the subject's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, subjects will be asked to sign and date the Informed Consent Form.

Subjects, or their legally authorized representatives, must give informed consent in writing prior to the performance of any protocol-specific procedure. Subjects who cannot give informed consent (i.e., mentally incompetent subjects or those physically incapacitated such as comatose subjects) are not to be recruited into the study. Subjects who are competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. A copy of the signed Informed Consent Form will be provided to the subject.

15.4. Subject Confidentiality

The Investigator must attempt to assure that the subjects' confidentiality will be maintained within the limit of the law. Subjects will be identified by subject number and initials (or other code) on all documents submitted to the Sponsor. Subjects will not be identified by name.

All records will be kept in a secure place in the clinical research site. Computer data entry and data review programs will be done using subject numbers and initials (or other code) only. Clinical information will not be released without written permission of the subject, as outlined in the subject consent form.

The Investigator must maintain a log of subject names and identification codes.

16. DOCUMENTATION

16.1. Study File and Site Documents

Prior to the activation of the study, at a minimum, the following items must be received by the Sponsor from the site:

1. Confidential Disclosure Agreement.
2. Signed protocol, and amendment(s) page(s).
3. The Investigator's curriculum vitae and current medical license. Note: Investigator or a Co-Investigator must be a medical doctor (MD).
4. Documentation of required training for designated behavioral counselors (e.g., nicotine or smoking cessation).
5. Signed Clinical Study Agreement/Contract.
6. Signed Financial Disclosure Form from the relevant site personnel.
7. IRB written approval for the protocol, amendment(s), Informed Consent Form, Smoking cessation information and advertisements (if applicable).
8. IRB Membership list or an official statement from the IRB stating the IRB is in compliance with Good Clinical Practice (GCP).
9. FDA Form 1572

16.2. Study Documents Supplied by the Sponsor

The Sponsor will supply the investigator with the following items:

1. Current version of the Investigator's Brochure.
2. Current version of study protocol.
3. Master CRF.
4. Informed Consent Form template.
5. Study Procedure Manual.
6. Laboratory Manual (if applicable).

16.3. Maintenance and Retention of Records

It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Investigators will be instructed to retain all study records required by the Sponsor and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on notification from the Sponsor:

1. For a period of at least 2 years from the **last** marketing approval worldwide.
2. Or a period of at least two years after discontinuation of clinical development of the investigational product as confirmed by the Sponsor.

The investigator will be instructed to consult with the Sponsor before disposal of any study records and to provide written notification to the Sponsor of any change in the location, disposition, or custody of the study files.

17. ADMINISTRATIVE PROCEDURES

17.1. Sponsor Responsibilities

The study will be monitored by representatives of the Sponsor and/or designated contract research organizations (CROs). Routine monitoring visits will be conducted to (at a minimum):

1. Assure compliance with the study protocol.
2. Verify that the research facilities, including laboratories and equipment, are adequate to safely and properly conduct the study.
3. Verify that the investigational product is stored properly and under the proper conditions, is in sufficient supply, and that receipt, use, and destruction or return of investigational product at the study sites are controlled and documented adequately.
4. Verify that written informed consent was obtained before any protocol-specific screening procedures are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the provision of study drug.
5. Review the subject CRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
6. Verify that the Investigator and study site personnel are adequately qualified throughout the study.
7. Verify that the safety information and amendments are submitted to the IRBs.

17.2. Investigator Responsibilities

All requested study data must be entered on the CRFs for the study. An explanation should be provided for all missing data. Correction of data on a CRF will be made with identification of the individual making the correction and date of the correction. Only individuals who are identified on the Delegation of Responsibility Form(s) may correct data on the CRF. For those subjects who withdraw before completion of their specified treatment regimen, all available efficacy and safety data must be entered in the CRF. The reason for withdrawal must be specified. Incomplete or inconsistent data on the CRFs will result in data queries that will be returned to the Investigator for resolution.

The Investigator must maintain adequate and accurate source documents upon which CRFs for each subject are based. The source documents are to be separate and distinct from the CRFs, except for cases in which the Sponsor has predetermined that direct entry into specified pages of the subject's CRF is appropriate. The documents to be maintained must include, but are not limited to, detailed notes on:

1. The medical history prior to participation in the study.
2. The basic identifying information, such as demographics, that link the subject's source documents with the CRFs.
3. The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
4. The subject's exposure to study treatment.
5. All AEs.
6. The subject's exposure to any concomitant therapy, including dates of administration.
7. All relevant observations and data on the condition of the subject throughout the study.
8. The oral and written communication with the subject regarding the study treatment, including the risks and benefits of the study. The date of informed consent must be recorded in the source documentation.

17.3. Regulatory Compliance

Quality Assurance representatives from the Sponsor or their delegate, and the FDA as required will be allowed to periodically visit the Investigators to discuss the conduct of the trial and, upon request, to inspect the records of the trial. These reviews are necessary to ensure that the study is conducted according to standards consistent with the ICH GCP Guidelines.

The Investigator agrees to discuss and correct, if necessary, any problems or deficiencies that are found during the course of these reviews.

17.4. Protocol Modification/Premature Termination

All protocol amendments must be written and approved by the Sponsor. Each IRB will review and approve amendments prior to their implementation in the study. IRB approval need not be obtained prior to removal of an immediate hazard to subjects.

The Sponsor may suspend or terminate the protocol early if safety or other issues occur. Furthermore, the study may also be terminated prematurely by the Sponsor for important corporate reasons, or due to instruction of the FDA due to safety reasons.

The Investigator may terminate participation at his/her site at any time but must provide all study data for subjects randomized.

Following a decision of temporary suspension or discontinuation, it is a responsibility of the Investigator to inform the study subjects and IRB stating the reasons for premature termination. The Sponsor shall be responsible for expedited reporting and/or notification to the FDA, as applicable.

17.5. Policy for Publication and Data Presentation

The Sponsor encourages the scientific publication of data from clinical research trials. However, Investigators may not present or publish partial or complete study results individually. The Investigators and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. Any manuscript or abstract proposed by the Investigators must be reviewed to

ensure accuracy of data represented and commented upon in writing by the Sponsor prior to submission for publication. Investigators agree to consider the comments of the Sponsor in good faith and the Sponsor agrees in good faith not to impose limitations on access to the complete study data or unreasonable or inappropriate restrictions on publication of the study results. In case of publication, confidentiality of the study volunteers will be maintained.

18. INVESTIGATOR'S AGREEMENT

Protocol No. ACH-CYT-10 (ORCA-V1)

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information submitted by the Sponsor relating to non-clinical and prior clinical experience to all personnel for whom I am responsible that participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (case report forms, shipment and drug return/destruction forms and all other information collected during the study) in accordance with the current GCP and local regulations.

_____

Site Principal Investigator's name

_____

Signature

_____

Date

_____

Institution

19. REFERENCES

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APPENDIX 1. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) provides a standardized method to assess both suicidal ideation and behaviour to identify those at risk for suicide.[21] The questionnaire must be administered by trained study staff at Screening and again at the Week 6 (Day 42) and End of Treatment (Day 86) study visits. Assessments at Screening will utilize the "Screening" version of the form with ideation to be assessed in the past 3 months and suicidal behaviour within lifetime (the later assessment timing helps to discern if later positive assessments are possibly treatment emergent). Any "Yes" to question 4 or 5 at screening or "Yes" to any suicidal behaviour question will be considered exclusionary for this study. Assessments at Week 6 (Day 42) and End of Treatment (Day 86) study visits will utilize the "Since Last Visit" version of the form with timeframe to be "since last assessment". Any "Yes" to question 4 or 5 or "Yes" to any suicidal behaviour question requires reporting as an AE as well as referral to a qualified Mental Health Professional for follow up.

*Training is to be documented via certification in past 1 year on the C-SSRS and may be updated or by reviewing the on-line training module provided by the developing author.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

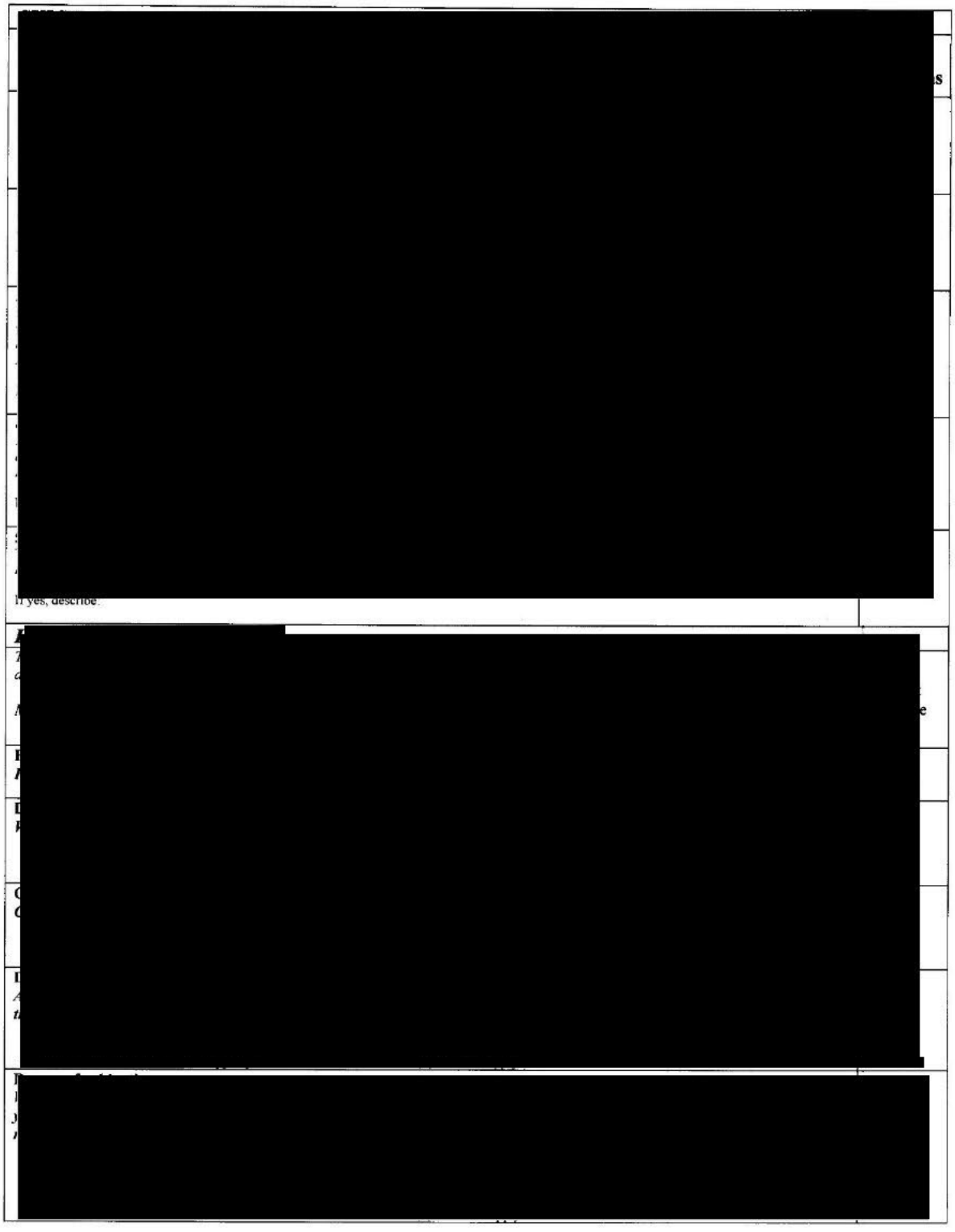
Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

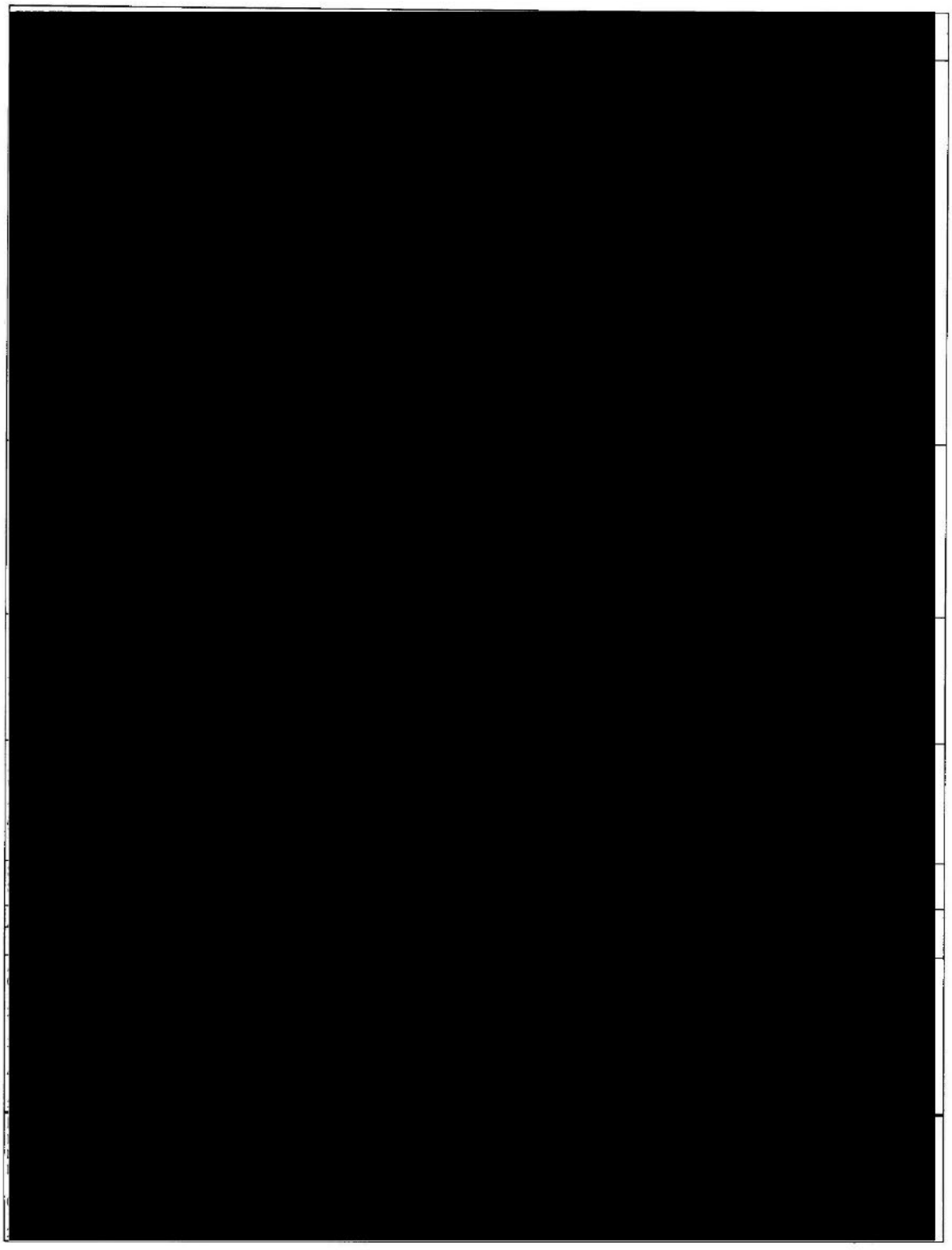
Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Screening - United States/English - Mapi.
ID040351 / C-SSRS-Screening_AU5.1_eng-USori.doc



C-SSRS—Screening (Version 1/14/09)
Page 1 of 2



C-SSRS—Screening (Version 1/14/09)
Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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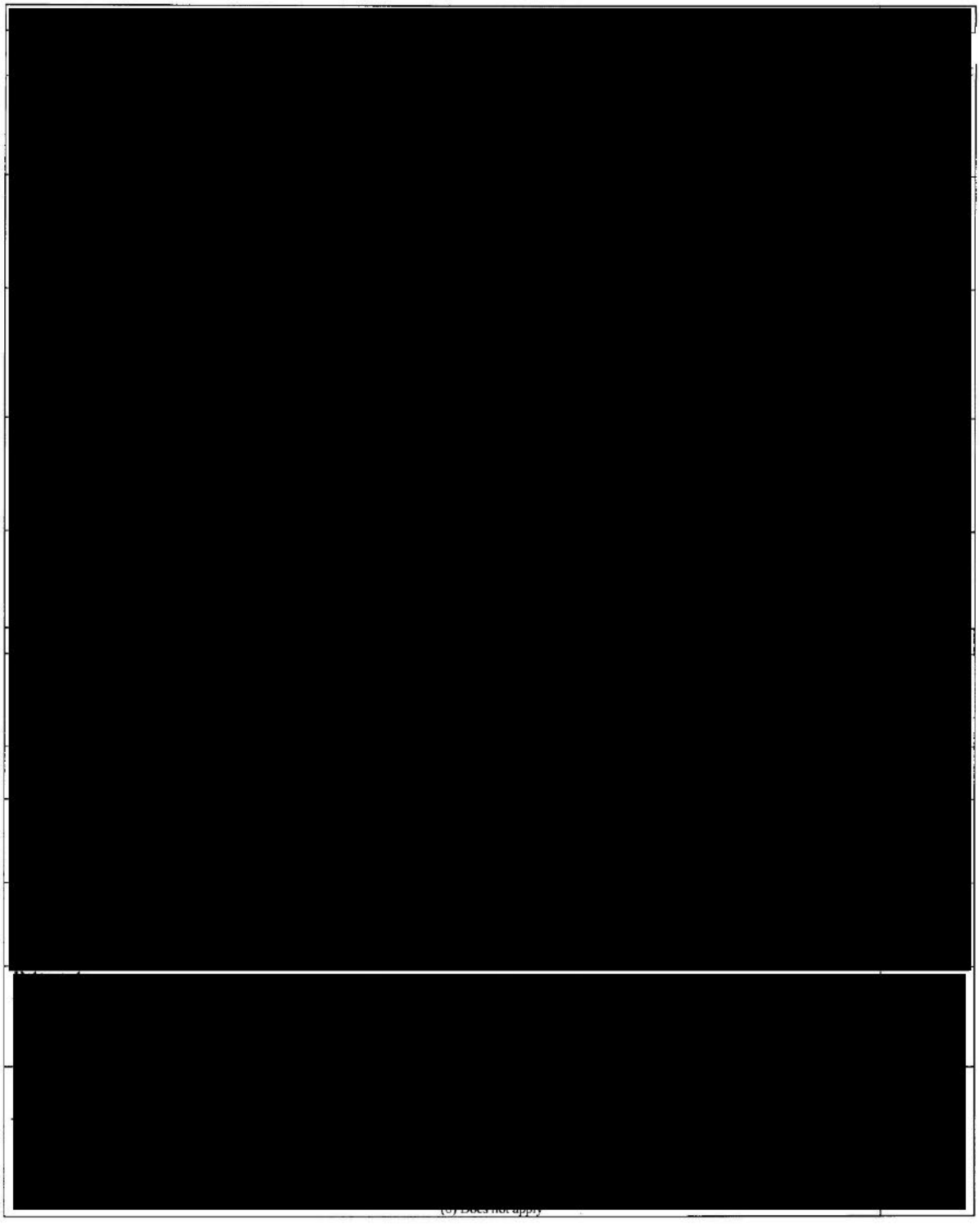
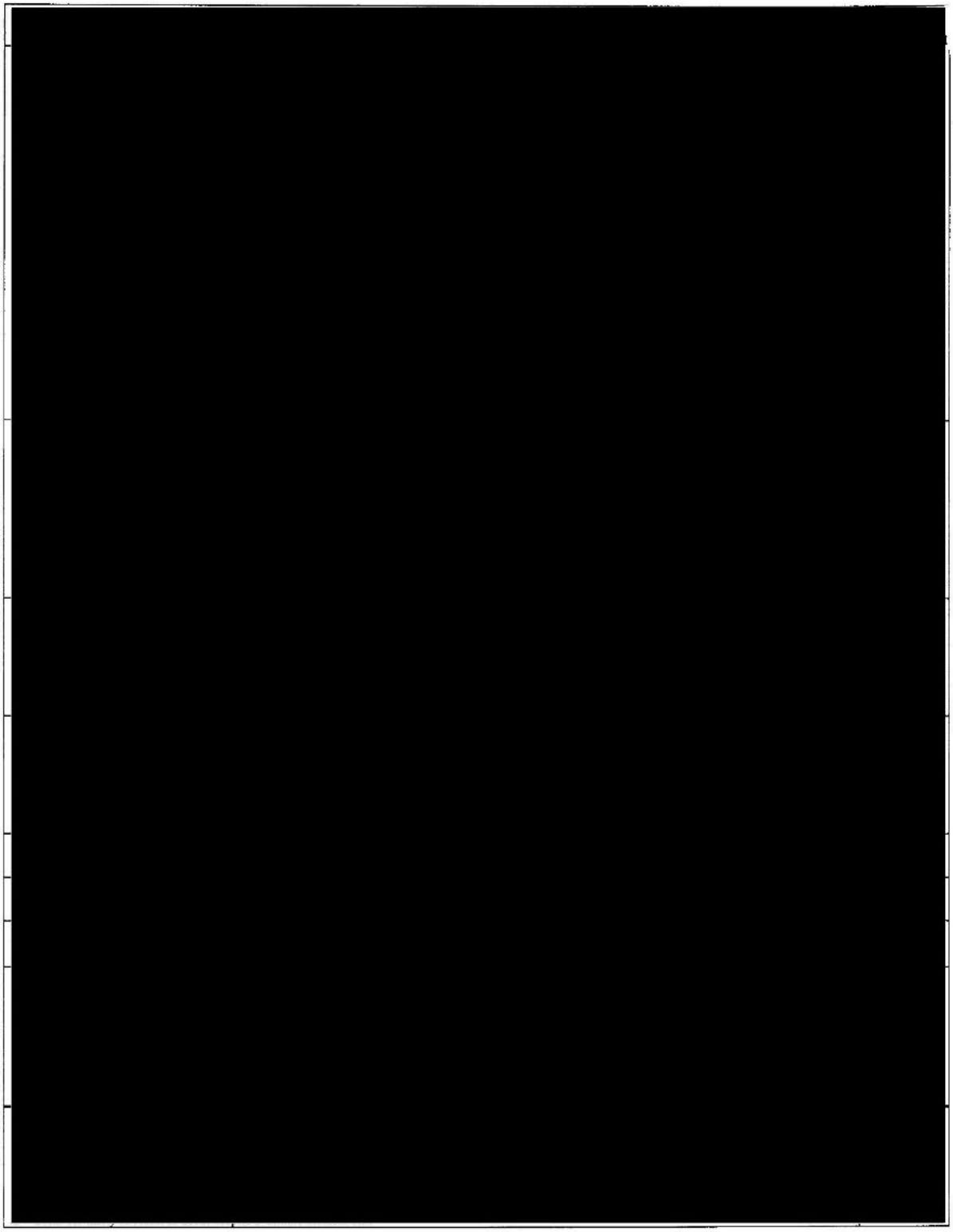


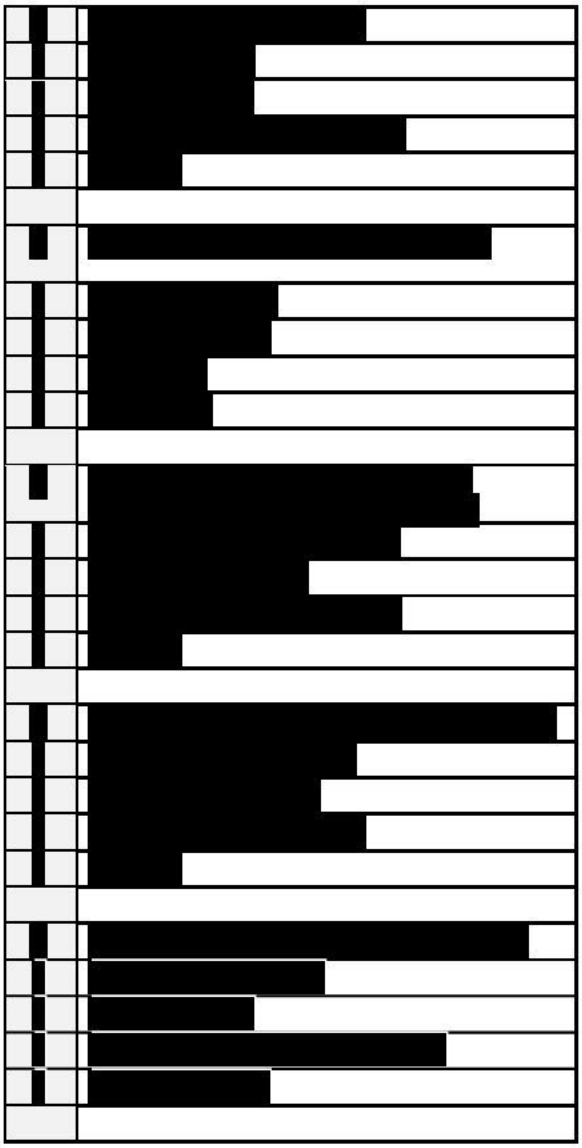
C-SSRS—Since Last Visit (Version 1/14/09)
Page 1 of 2

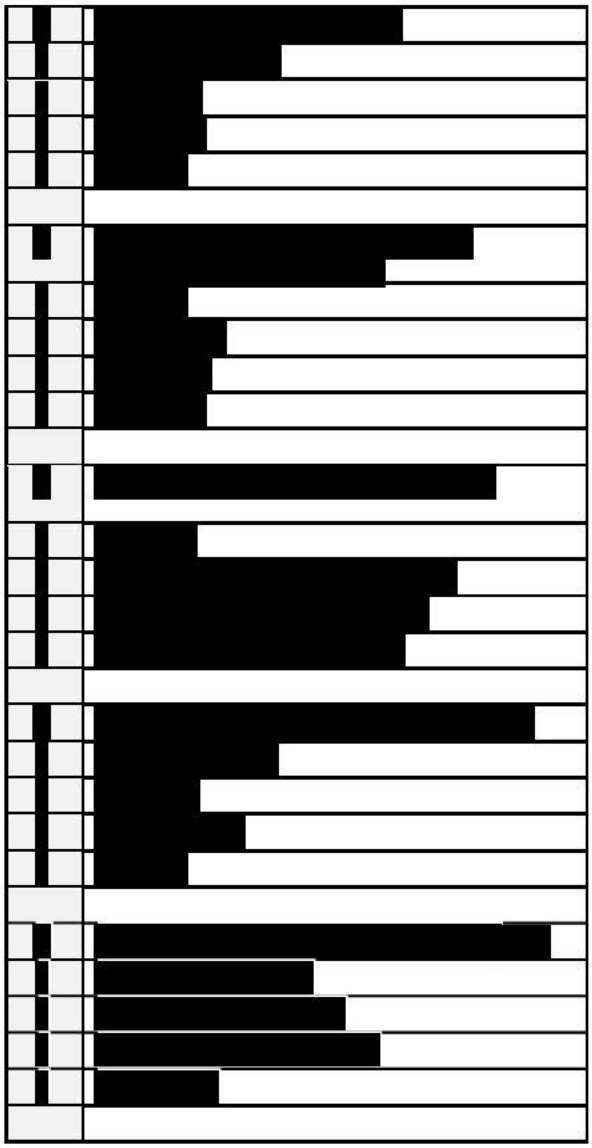


C-SSRS—Since Last Visit (Version 1/14/09)
Page 2 of 2

APPENDIX 2. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

The HADS questionnaire[22] has been validated as a self-report instrument to measure levels of anxiety and depression and will be administered to study subjects. This questionnaire must be completed by all potential study subjects (completed = each of the 14 questions must be answered by the subject) during screening. The HADS questionnaire must be reviewed by clinic staff and a summation score calculated by totalling the numbers circled for each question at Screening Visit #1. A score $\geq$11 (total of Depression "D" Questions only) indicates current symptoms of moderate to severe depression and would confirm study exclusion #10. The HADS questionnaire is to also be completed at Day 42 (Week 6) and again at Day 86 (Week 12). Analysis of results is outlined in the study Statistical Analysis Plan.





Note: The actual questionnaire will not indicate the category (A=anxiety, D=depression) or the points, which are provided here to show how responses will be scored for analysis.

APPENDIX 3. PENN STATE ELECTRONIC CIGARETTE DEPENDENCE INDEX

The PennState Electronic Cigarette Dependence index (PSECD) -10 questions,[16] must be administered at Screening, Week 6, and Week 12 and completed by the study subject.

1. How many times per day do you usually use your electronic cigarette? (assume one "time" consists of around 15 puffs, or lasts around 10 minutes) _____ per day
2. On days that you can use your electronic cigarette freely, how soon after you wake up do you first use your electronic cigarette? _____ minutes
3. Do you sometimes awaken at night to use your electronic cigarette?

   □ Yes □ No
4. If yes, how many nights per week do you typically awaken to do so? _____ nights
5. Do you use an electronic cigarette now because it is really hard to quit (using e-cigs)?

   □ Yes □ No
6. Do you ever have strong cravings to use an electronic cigarette?

   □ Yes □ No
7. Over the past week, how strong have the urges to use an electronic cigarette been? (check one)

   □ No urges
   □ Slight
   □ Moderate
   □ Strong
   □ Very strong
   □ Extremely strong
8. Is it hard to keep from using an electronic cigarette in places where you are not supposed to?

   □ Yes □ No

When you have not used an electronic cigarette for a while, OR when you tried to stop using one:

9. Did you feel more irritable because you couldn't use an electronic cigarette?

   □ Yes □ No
10. Did you feel nervous, restless, or anxious because you couldn't use an electronic cigarette?

    □ Yes □ No

APPENDIX 4. MARIJUANA CRAVING QUESTIONNAIRE (MCQ-SHORT FORM)

The 12-item marijuana craving questionnaire (MCQ-Short Form) was derived from a 47-item questionnaire and validated to provide reliable measurement of marijuana craving.[23] The MCQ-Short Form will be collected at the second Screening Visit (SV2) and again at the Week 12 regardless of whether or not a study subject indicates she/he smokes marijuana. Individual scores recorded in the case report form. Analysis of results will assess 4 factors (compulsivity, emotionality, expectancy, purposefulness) by grouping questions. Details related to analysis are outlined in the Statistical Analysis Plan.

Indicate how strongly you agree or disagree with each of the following statements by placing a check mark in one of the spaces between STRONGLY DISAGREE and STRONGLY AGREE. The closer you place your check mark to one end or the other indicates the strength of your agreement or disagreement. If you don't agree or disagree with a statement, place your check mark in the middle space (4). Please complete every item. We are interested in how you are thinking or feeling **right now** as you are filling out the questionnaire.

	Question	**Response**						
		Strongly Disagree……..Strongly Agree						
		1	2	3	4	5	6	7
1	Smoking marijuana would be pleasant right now.	○	○	○	○	○	○	○
2	I could not easily limit how much marijuana I smoked right now.	○	○	○	○	○	○	○
3	Right now, I am making plans to use marijuana.	○	○	○	○	○	○	○
4	I would feel more in control of things right now if I could smoke marijuana.	○	○	○	○	○	○	○
5	Smoking marijuana would help me sleep better at night.	○	○	○	○	○	○	○
6	If I smoked marijuana right now, I would feel less tense.	○	○	○	○	○	○	○
7	I would not be able to control how much marijuana I smoked if I had some here.	○	○	○	○	○	○	○
8	It would be great to smoke marijuana right now.	○	○	○	○	○	○	○
9	I would feel less anxious if I smoked marijuana right now.	○	○	○	○	○	○	○
10	I need to smoke marijuana right now.	○	○	○	○	○	○	○
11	If I were smoking marijuana right now, I would feel less nervous.	○	○	○	○	○	○	○
12	Smoking marijuana would make me content.	○	○	○	○	○	○	○

APPENDIX 5. BEHAVIORAL SUPPORT

Each participating site must have at least two or more staff members experienced and qualified to provide nicotine cessation counseling. Study site counselors who provide behavioral support during this study are required to have either a master's level or higher degree in some sort of counseling profession (e.g., health educator, chemical dependence counselor) or completed a nicotine treatment training course of at least 4 hours.

All subjects will receive up to 14 behavioral support sessions by a qualified study site staff member, starting prior to randomization at the Screening Visit #2 when the subject sets their Quit Date, again at randomization and continuing through the End of Treatment (Day 86±1 day) visit. Each behavioral session will be subject-driven and must include direct engagement with the subject about their attempt to quit nicotine vaping. Each session should last up to 10 minutes.

Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they quit vaping as planned or if they lapse and use an e-cigarette after their quit date during the Treatment Period. It is important for subjects to keep trying to quit as planned. It is also important to stress to subjects that they should be honest when reporting their e-cigarette status and to remind them that all timepoints from Week 2 through Week 12 during the Treatment Period will be verified using cotinine levels.

Subjects will receive additional abbreviated support (based on issues/concerns/questions raised by the subject) during the Follow-up Period.

Each behavioral session will be subject-driven and must include direct engagement with the subject about their attempt to quit vaping. Counselors must be warm, empathetic, and genuine so that the subject is comfortable and will share issues and challenges that can be discussed further. In addition, the counselor is to be well-versed on study drug administration and expected side effects of cytisinicline and able to clearly review and discuss these topics with the study subject. Subjects will be encouraged to "keep trying" if they experience set-backs or a "lapse" during treatment. Each session should last up to 10 minutes.

Practical counseling (problem solving/skills training) should be given. Topics include, but are not limited to, the following:

- Abstinence–Striving for total abstinence is essential. Not even a single puff after the quit date.
- Past quit experience–Identify what helped and what hurt in previous quit attempts. Build on past success.
- Anticipate triggers or challenges in the upcoming attempt–Discuss challenges/triggers and how the subject will successfully overcome them (e.g., avoid triggers, alter routines).
- Alcohol–Because alcohol is associated with relapse, the subject should consider limiting/abstaining from alcohol while quitting. (Note that reducing alcohol intake could precipitate withdrawal in alcohol-dependent persons).
- Other smokers or vapers in the household–Quitting is more difficult when there is another smoker/vaper in the household. Subjects should encourage housemates to quit with them or to not smoke/vape in their presence.

- Recognize danger situations–Identify events, internal states, or activities that increase the risk of vaping or relapse (i.e., e-cigarette cues and availability of e-cigarettes or other nicotine-containing vaping devices, experiencing urges).
- Develop coping skills–Identify and practice coping or problem solving skills. Typically, these skills are intended to cope with danger situations (i.e., learning to avoid temptation and triggers).
- Provide basic information–Provide basic information about nicotine addiction and successful quitting.

Worksheets containing questions will be provided and may be administered by the counselor to initiate/foster open conversation with the subject and may be used at the start or during the study. These questions do not need to be used at every visit. They are provided as guidance if the subject has difficulty opening up a discussion.

Potential questions are:

- What is my motivation for quitting?
- Why is it important for me to quit right now?
- What are the biggest barriers I will encounter without an e-cigarette?
- What are some alternatives I can do when I face these barriers instead of using nicotine?
- What are my stress triggers for cravings?
- How will I deal with these stressors instead of vaping or using nicotine?
- What are your biggest concerns/fears about quitting vaping or using nicotine?

At the end of each visit, the subject will be reminded of supplementary information for additional support including: study staff contact information, Quitline information (1-800-QUIT-NOW), or additional websites.

Any questions regarding the medication or protocol must be answered by qualified study staff. Documentation of the behavioral support must be captured in the subject's source document.

APPENDIX 6. MINNESOTA WITHDRAWAL SCALE (MNWS)

Several versions of the Minnesota Withdrawal Scale (MNWS) have been used since 1986. The version used in this study has been shown to provide specific assessment of nicotine withdrawal using 9 specific items.[24,25] The questionnaire will be administered to all study subjects on Week 1, Week 2, Week 3, Week 4, and twice around the Week 12 visit (first to be 3 days (+/- 1 day) prior to the Week 12 visit and again 3 days (+/- 1 day) after the Week 12 visit). Analysis of results is outlined in the study Statistical Analysis Plan.

For each of the following, please rate yourself on how you have been feeling over the past 24 hours. Mark the number that applies to you:

Question	Response				
	Not at all	**Slight**	**Moderate**	**Quite a bit**	**Extreme**
Urge to vape item 1	0	1	2	3	4
Depressed mood item 2	0	1	2	3	4
Irritability, frustration, or anger item 3	0	1	2	3	4
Anxiety item 4	0	1	2	3	4
Difficulty concentrating item 5	0	1	2	3	4
Restlessness item 6	0	1	2	3	4
Increased appetite item 7	0	1	2	3	4
Difficulty going to sleep item 8	0	1	2	3	4
Difficulty staying asleep item 9	0	1	2	3	4